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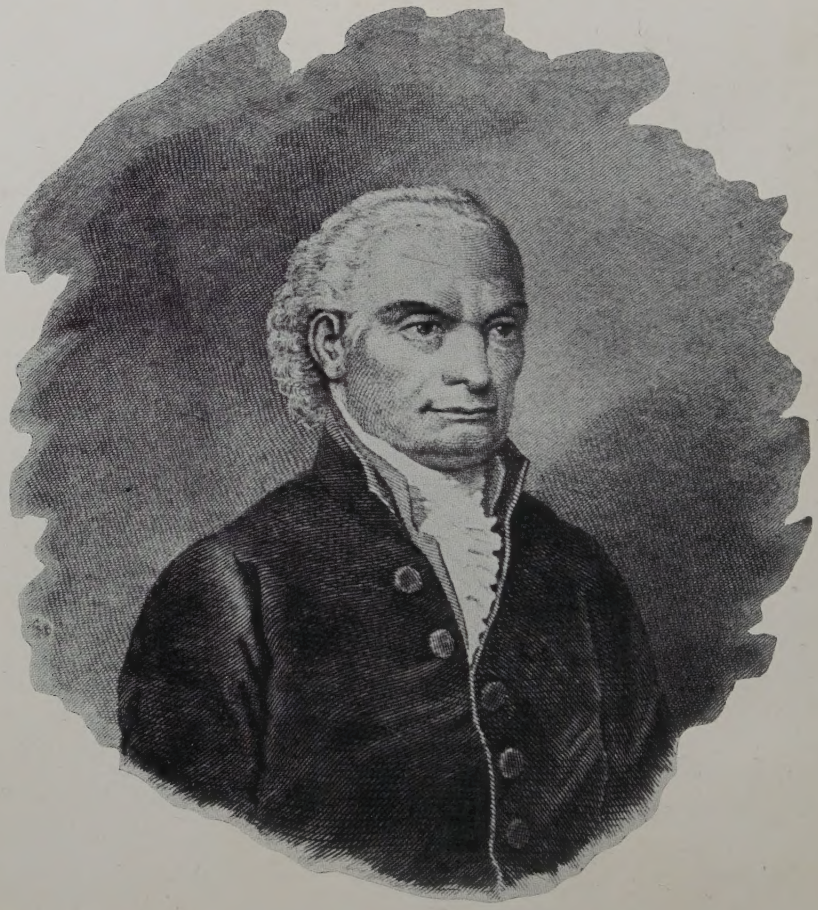

DOMENICO COTUGNO
1736-1822

Da un ritratto in miniatura fatto dal vivo

CEREBROSPINAL FLUID

IN HEALTH AND IN DISEASE

BY

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WITH FOREWORD BY

LUDVIG HEKTOEN, M.D.

WITH EIGHTY-EIGHT ILLUSTRATIONS, INCLUDING FIVE COLOR PLATES

THIRD EDITION, THOROUGHLY REVISED

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To Him to Whom the Practice of Medicine Constitutes an Ideal Rather Than a Profession,

To Him Who Combines Clinical Insight and Scientific Research,

To Him Who Sees in Medicine Both a Science and a Philosophy,

This Little Volume is Respectfully Dedicated.

FOREWORD

By Ludvig Hektoen, M.D.

The author was kind enough to ask me if I would look over his manuscript and then tell him whether it seemed to me worthy of publication. Later, when I told him that in my opinion he had produced a valuable little book, he requested me to state the reasons for this favorable opinion in the form of a foreword. This I can do in a few brief statements.

In the first place, on reading the manuscript, I soon became aware that the author had come to his task with not only a large experience behind him in the examination by various methods of the cerebrospinal fluid as an aid in diagnosis, but with a highly creditable record in the scientific study of this fluid as well. Evidently he had been drawn to his work on the cerebrospinal fluid because of its attractiveness as a field of research, as well as on account of its importance in diagnosis.

It is to this happy combination of true philosophic interest and first-hand practical knowledge on the part of the author that the book owes its chief merit, namely, thoroughness and freshness in the parts dealing with fundamental problems, as well as in those dealing with practical matters. In the second place there could be no doubt in regard to the timeliness of a work of this kind. Indeed it seemed to me that a definite want would be supplied; for, in spite of an increasing importance in medicine, there was as yet no comprehensive book on all phases of the cerebrospinal fluid.

John McCormick Institute
For Infectious Diseases, Chicago, 1919.

PREFACE TO THIRD EDITION

The constantly increasing interest of clinicians and research workers in the study of cerebrospinal fluid has been a source of gratification to me. It has made the preparation of a third edition of this book a "labor of love" in spite of the enormous amount of work entailed.

In this edition I have tried to keep pace with the development of the subject and have endeavored to incorporate both the results of other workers in the field and my own recent investigations. I have attempted to do this in as compact a form as possible to obviate the necessity of adding unduly to the length of the book.

In order to simplify the reading of this volume, I have rearranged the chapters, separating the clinical from the theoretical sections of the book. With the same thought in mind, I have tried to present the simplest methods to be employed by the practicing physician.

I wish to acknowledge my indebtedness to Dr. R. L. Kahn, the author of the Kahn test, for his brief description of his test.

I also wish to express my thanks to Dr. M. A. Perlstein for the valuable assistance he has rendered in the preparation of the third edition of this book.

Chicago, Ill., 1929.

A. Levinson.

PREFACE TO THE SECOND EDITION

The welcome given the first edition of this book by medical reviewers as well as by the medical profession at large has encouraged me to undertake a second edition.

I have taken this opportunity to incorporate the results of the most recent research on cerebrospinal fluid. The

addition of new data and the revision of old has necessitated the recasting of some chapters. Several old illustrations have been discarded and many new ones have been added. Some of the methods of examination have been simplified for practical use. References have been brought up to date, and wherever possible errors have been corrected.

A. Levinson.

Chicago, Ill., 1923.

PREFACE TO FIRST EDITION

Of recent years the study of body fluids has been engaging the attention of many physicians and scientists. Particularly marked has been the interest in the study of cerebrospinal fluid. Through recent investigations of this fluid, we have gained a great deal of information regarding the diagnosis and nature of many diseases and a much clearer conception of the general physiologic processes in the body. Further investigations on the subject will open up new possibilities in science and medicine, for there is hardly another body fluid that presents so favorable an opportunity for the study of physiologic and pathologic processes in the human body as the cerebrospinal fluid.

Cerebrospinal fluid is of great physiologic importance for various reasons. It is the clearest and most transparent of all the fluids of the body. It is clearer than blood, than bile, and even clearer than urine, and under normal conditions experiments may be made on it without fear of clot formation or color change. Furthermore, cerebrospinal fluid, like blood and urine, can be removed from the living body without injury to the system. This gives one the opportunity of working with processes in the living body—a distinct advantage over the study of dead tissue.

From the standpoint of pathology also, cerebrospinal fluid presents an exceptional opportunity for study. The slightest change in the color of the fluid, the smallest increase in the protein content or in the cell count, all of which are easily discernible, indicate the presence of a pathologic process. One is able to follow the course of disease throughout all stages by noting the various changes the cerebrospinal fluid undergoes from time to time. These changes may be manifested not only by the presence of the causative organisms themselves, but just as frequently by specific physical, chemical, cytologic and physicochemical processes. A close study of the changes in the cerebrospinal fluid under pathologic conditions throws light, not only on the specific diseases of the nervous system, but on the condition of other systems. One can readily see, therefore, how large is the scope for the study of cerebrospinal fluid.

In this book I shall discuss cerebrospinal fluid in its various phases, and shall attempt to show the nature of the fluid in its normal state and to point out the deviations in processes of disease. I shall incorporate the results of my own clinical and experimental studies as well as the observations of the many workers who have added to our knowledge by their researches on cerebrospinal fluid.

This little book is sent out as an humble contribution, as I am fully aware of its many shortcomings and omissions; but if it saves the busy practitioner the irksome task of consulting countless sources for information on cerebrospinal fluid, I shall feel that the work has not been in vain. And if perchance it should serve to stimulate even one zealous student to help solve some of the problems presented, I shall feel that my effort has been amply rewarded.

Many of the investigations that have found their way into this volume would not have been possible without the constant cooperation of certain institutions and individuals. I, therefore, take this opportunity of expressing my

gratitude to them collectively and individually—to the attending staff, internes and nurses of the Michael Reese Hospital in general, and the Sarah Morris Hospital for Children in particular, to Dr. Katharine Howell, serologist of the Nelson Morris Institute for Medical Research, to Professor F. C. Becht of the Department of Pharmacology of the Northwestern University, and to Dr. G. Bartelmez of the Department of Anatomy, University of Chicago.

Particular thanks are due to Professor Ludvig Hektoen of the University of Chicago for his helpful suggestions and for his careful reading of the manuscript, and to Professor Shiro Tashiro of the Department of Biochemistry of the University of Cincinnati for his tireless assistance in checking up many of the experiments. Thanks are also due the editors and publishers of the many journals for their permission to republish some of my articles that appeared in their journals.

A. Levinson.

Chicago, Ill., 1919.

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CEREBROSPINAL FLUID

CHAPTER I

HISTORY OF CEREBROSPINAL FLUID

The history of our knowledge of cerebrospinal fluid may conveniently be divided into the following periods:

1. Knowledge of the existence of cerebrospinal fluid in pathologic conditions.
2. Discovery of the existence of the fluid in normal individuals.
3. Investigations concerning the physiology of cerebrospinal fluid.
4. Discovery of methods of removing fluid from the living.
5. Modern research on cerebrospinal fluid.

KNOWLEDGE OF EXISTENCE OF CEREBROSPINAL FLUID IN PATHOLOGIC CONDITIONS

The existence of water on the brain in pathologic cases was known to the ancients. Hippocrates (460-370 B. C.) is credited with tapping the ventricles in hydrocephalus. We have nothing to show, however, that the ancients knew of the existence of fluid in normal persons. There is no mention of cerebrospinal fluid in the early writings of Hippocrates. In the later Hippocratedian collection the brain is spoken of as a gland. The glandular nature of the brain in this instance, however, does not refer to the secretion of cerebrospinal fluid, but to the so-called secretion which the ancients believed was poured down from the brain into the pharynx. Herophilus (280 B. C.) the discoverer of the torcular Herophili and of the fourth ventricle of the brain,

knew of the existence of the chorioid plexus but does not mention its function or the contents of the ventricles. It is but natural to suppose that Herophilus who dissected hundreds of human bodies should have known of the existence of cerebrospinal fluid in the ventricles. Yet, in giving a description of the ventricles which he speaks of as the

Fig. 1-*A*.—Leonardo da Vinci's conception of brain ventricles.

seat of the soul, he makes no reference to the presence of any fluid in the brain. There is a possibility, of course, that the lost books of Herophilus may have contained some reference to cerebrospinal fluid.

One finds the same silence on the subject in other ancient authorities. Erasistratus of Julis (330-250 B. C.) describes

four cavities in the brain, but he makes no mention of fluid in them. Hemesius of Emersa (born 340 A. D.) gives a minute analysis of the ventricles and the localization of mental power within them, but he does not speak of the fluid they contain. Galen (131-201 A. D.), however, who

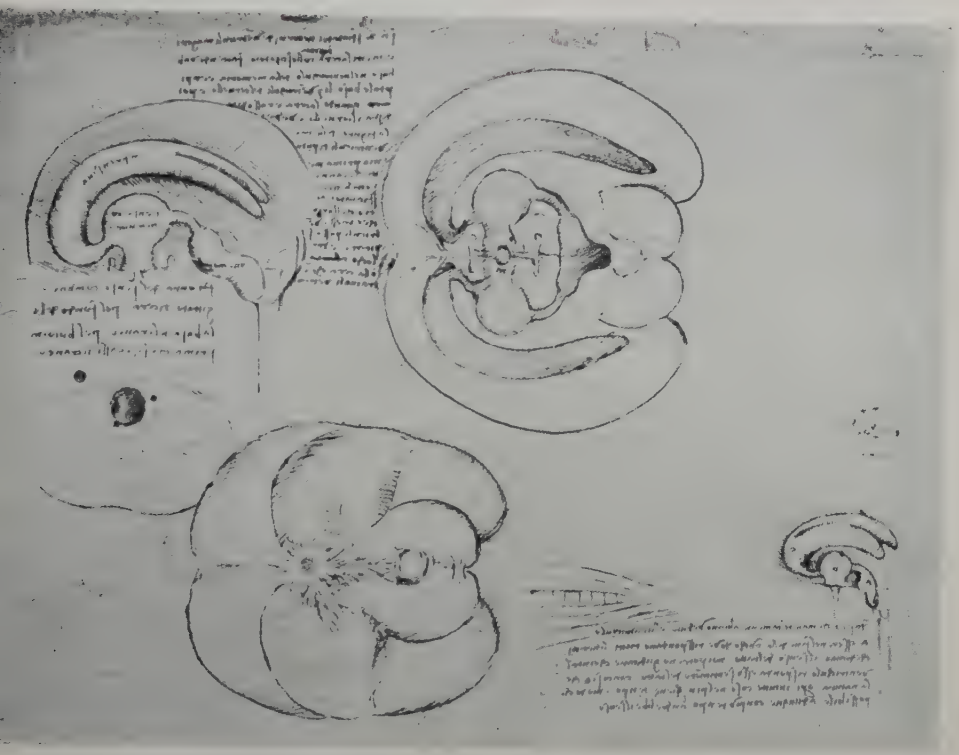

Fig. 1-*B*.—Leonardo da Vinci's conception of brain ventricles.

was thoroughly familiar with the construction of the ventricles, speaks of an "excrementitial liquid, expressed from several places in the brain into the ventricles, especially the fourth, where this liquid is stored and then purged into the nose through the ethmoid bones and infundibulum." The fluid referred to was probably the cerebrospinal fluid.

One would naturally turn to Vesalius for a description of cerebrospinal fluid, for it is a well-known fact that Vesalius knew the chorioid plexus and, therefore, may also have observed the fluid. Yet, though he devotes page after page to a discussion of the localization of the soul, he merely mentions a watery humor of the brain, but gives no description of any humor that would indicate that he had the cerebrospinal fluid in mind. Mention of the presence of a fluid in the brain is found in the writings of Varolius (1543-1575). This scientist, who described the pons that bears his name, denied the existence of pneuma in the ventricles, and insisted that it was fluid and not air that filled up the cavity of the ventricles. However, he gives no description of the fluid he saw.

Drawings by Leonardo da Vinci (1452-1519) show that he knew of the ventricles of the brain (Figs. 1-*A* and 1-*B*), but there is no evidence to prove that he knew of the existence of fluid within them.

The absence of a method whereby normal cerebrospinal fluid could be demonstrated in living beings was responsible for the apparent lack of interest shown in the investigations of this fluid. Whatever interest was manifested, was confined to pathologic cases.

Francis Glisson (1597-1677) says, "In some Bodies that we have dissected between the Dura and Pia Mater, and in the very ventricles of the Brain, we have found wheyish and waterish humors; from whence it is manifest, that this affect is complicated with the Hydrocephalus.

"We have found the Brain in others that we have opened, to be firm and inculpable, and not overflowed with any waterish congestions."

In 1727 Stalpartius Vander Wiel described a case of injury to the head in which a clear watery fluid was seen to escape from the ear for several days after the injury. In 1764 Robert Whytt published a description of tuberculous meningitis. He divided the disease into three stages according to the behavior of the pulse, and attributed the

various manifestations of the disease to the presence of a serous exudate in the brain. In 1768 he published the results of his work on acute hydrocephalus under the title "Observations on Dropsy of the Brain." Under the heading of acute hydrocephalus he included all forms of acute brain disease.

DISCOVERY OF THE EXISTENCE OF CEREBROSPINAL FLUID IN NORMAL INDIVIDUALS

A discussion of cerebrospinal fluid in normal persons is first contained in the writings of Albertus de Haller (Fig. 2). In the "First Lines of Physiology" in the English translation of the third Latin edition, we find the following:

"The fluids, which, being deposited from the blood into other vessels, are said to be secreted, seem reducible to four classes. The first consists of viscid fluids, coagulable by a heat of about 150°, by alcohol, and by strong acids; although generally, in the living animal, they escape in the form of vapor and after death are compacted into a gelatinous substance. To this class belong the liquor and halitus of the ventricles of the brain, the pericardium, pleura, peritoneum, tunica vaginalis, amnois, joints, renal capsules, and probably of the womb, with the juices of the stomach and intestines, and lastly the lymph generally known."

A little further Haller goes on as follows:

"Have lymphatic vessels been seen with certainty in the brain? They have been described in the large choroidal plexus amongst the fibers of the olfactory nerve, and in the pia mater. For my own part, I have never seen them, and it is probable that there are none, since there are no conglobate glands in the brain, which are always found near these vessels. As for the various accounts which are given of the pituitary glands, of the infundibulum and of the ducts which lead from thence into the veins of the head, absorbing water from the ventricles, they are not sup-

ported by any anatomic demonstration; which makes it probable that the vapor, which is secreted into the ventricles of a healthy person, is, in like proportion, absorbed again by the inhaling veins; and that if there be any excess, it descends through the bottom of the ventricles to the basis of the skull, and into the loose cavity of the spinal marrow. That this is the case, appears from the palsies, which ensue after apoplexies and from the watery tumors in the lower part of the spinal marrow, in hydrocephalic patients."

Fig. 2.—Albertus de Haller (1708-1777).

It is evident from Haller's statement that he knew of the existence of cerebrospinal fluid in the ventricles, although he spoke of it as a vapor.

Haller thought that the fluid or vapor also flowed into the small tubes of the nerves. In the quotation that follows may be found part of Haller's explanation of the mechanism of irritability, the original conception of which was advanced by Glisson.

"Upon the whole, it seems to be certain that, from the vessels of the cortex, a liquor is secreted into the hollow

tubes of the medulla, which, being continued into the small tubes of the nerves, and propelled to their extremities, is the cause of both sense and motion. But there will be a twofold motion in that humor; the one slow and constant from the heart; the other, not continual, but exceedingly swift, which is excited either by sense or any cause, as motions arising in the brain."

The discovery of cerebrospinal fluid in normal *living* animals should be attributed to Cotugno (1736-1822) (frontispiece), who is responsible for many discoveries in medicine. He discovered intestinal lesions postmortem in a patient who died of typhoid fever; he demonstrated the presence of albumin in urine on boiling; and he discovered the aqueduct in the internal ear known subsequently as the aqueductus Cotugnii. In his "*De Ischiade nervosa Commentarius*," Chapter IX, he states (translation by Professor Neuburger): "The whole space between the dura mater and the medulla is always filled; not by the medulla which is more turgescent in the living, nor by a water vapor (as this yet obscure substance is suspected of being by noted authors); but by water, similar to that about the heart which the pericardium holds, which fills the ventricles of the brain and the labyrinths of the ear, as well as the other free cavities of the body inaccessible to air." Cotugno believed that during life there was a liquid present and not a water vapor which after death became condensed into a liquid, because of the great amount of liquid present postmortem. He attributed the failure of earlier investigators to observe and to study the fluid to their faulty technic of dissection, wherein during the removal of the skull from the neck, the spinal cord coverings were torn, with subsequent escape of the fluid. He then describes a method of dissection which eliminates this difficulty, and by means of which he was able to collect in twenty cases between four and five ounces of cerebrospinal fluid. Cotugno then states that although the presence of fluid in man during life cannot

be proved beyond a doubt, nevertheless, in living fishes and turtles he has found considerable amounts of fluid. He did not, however, detect its presence in dogs or birds.

Although Cotugno usually gets the credit for the discovery of cerebrospinal fluid in normal living subjects, Bilanchoni claims that Valsalva prior to Cotugno found "an ounce of a certain liquid in cutting the cord membrane of a dog, a fluid resembling that seen in articulations."

INVESTIGATIONS CONCERNING THE PHYSIOLOGY OF CEREBROSPINAL FLUID

It was left to Magendie (Fig. 3) (1825) to give us an accurate description of the workings of the fluid, especially the fluid at the base of the brain. We are indebted to him for a clear-cut description of the physical appearance and protective function of the cerebrospinal fluid. The following is taken from Magendie's treatise on *Physiology:*

"But there is a disposition unknown to Bichat, which I have recently discovered, and which contributes in a manner extremely efficacious to the conservation and defense of the medulla.

"The canal which is formed around the medulla by the pia mater, and which is lined by the arachnoid, is a great deal larger than is necessary to contain the organ; but during life the whole interval is filled up by a serous liquid, which strongly distends the membrane and which spouts out to many inches in height from a small puncture made in the dura mater. An analogous arrangement is also to be observed around the brain and cerebellum. It is easy to conceive how efficacious must be the protection thus derived from the liquid which surrounds the spinal marrow, and in the midst of which it is suspended like the fetus in utero; with this difference that it is fixed in its position by the ligamentum dentatum, and the different spinal nerves.

"Besides the different envelopes of the brain of which we have spoken, and the dura mater which covers it in its whole extent, this substance is everywhere surrounded with a very fine serous membrane the principle use of which is to yield a thin fluid, which lubricates the brain. The arachnoid penetrates to all the cavities of the brain."

It is evident, therefore, that Magendie knew not only of the existence and appearance of the cerebrospinal fluid, but

Fig. 3.—François Magendie (1783-1855).

that he was also aware of the most significant function of the fluid—namely, its protective nature.

As soon as Magendie opened the way for the study of cerebrospinal fluid, a number of other investigators followed in his path. Luschka and Eckar studied the fluid from an anatomic standpoint. Cavazzani performed numerous experiments on dogs to determine the physiologic character of the cerebrospinal fluid. Naunyn made a study of the physics of cerebrospinal pressure. Shortly after, in 1842, Langet's *Anatomy and Physiology of the Nervous*

System appeared, and in it were nine pages devoted exclusively to a discussion of cerebrospinal fluid—a discussion that was both lucid and graphic.

Almost simultaneously speculation began as to the source of cerebrospinal fluid. Carl Schmidt, in 1850, expressed the view that the cerebrospinal fluid was not a mere transudate from the blood. Faivre, in 1853, advanced the theory that the fluid was a secretion. Numerous investigations followed the promulgation of this idea, and hundreds of experiments were undertaken by anatomists, pathologists, physiologists, and chemists, experiments that are being carried on to this very day.

DISCOVERY OF METHODS OF REMOVING CEREBROSPINAL FLUID FROM THE LIVING

With the discovery of a method whereby cerebrospinal fluid could be removed from the living body, a new era was ushered into the history of this fluid. One of the first means of obtaining the cerebrospinal fluid was by removing it from the skull. This operation was fraught with many difficulties. It involved the use of a great number of instruments and necessitated trephining of the skull and the making of a scalp wound.

In 1885, Corning injected 20 minims of a 2 per cent solution of hypochlorate of cocaine into a space situated between the spinous processes of two of the inferior dorsal vertebrae of a dog. Five minutes after the injection there were marked evidences of incoordination in the posterior extremities. A few minutes later there was pronounced weakness in the hind legs, but there were no signs of feebleness in the anterior extremities. The faradic current showed that there was no reflex action of the hind legs, but the anterior extremities responded quickly.

Corning then injected 30 minims of a 3 per cent solution of cocaine hypochlorate between the spinous processes

of the eleventh and twelfth dorsal vertebræ, in a man suffering from "spinal weakness." As there was no numbness noticeable, he injected 30 minims more in the same spot about six or eight minutes later. In ten minutes the man complained that his legs felt "sleepy," and brush applications showed that sensibility was greatly impaired.

As a result of his experiments Corning came to the conclusion that local medication by means of spinal puncture could prove of great therapeutic value in relieving a number of morbid conditions of the cord. Unfortunately, however, Corning left us neither a description of the technic he employed nor of the type of needle he used. Moreover, his operation was attended with a great degree of risk in that he introduced the needle too high up in the spinal column, thus incurring the danger of injury to the cord.

In 1891 W. Essex Wynter reported the drainage of cerebrospinal fluid in four cases of tuberculous meningitis. He treated his first case in 1889, making an incision in the skin of a patient suffering from tuberculous meningitis. In the incision which was made a little to one side of the spine of the second lumbar vertebra, he introduced a Southey tube and a trocar. When he felt that the point of the trocar had struck against the lamina, he directed it slightly downward, forced it through the ligamentum and theca, and then inclined it toward the median line. When the trocar was withdrawn, clear fluid rushed out into the Southey tube. A fine, India-rubber tube was then connected to facilitate continuous drainage. The symptoms of the disease subsided immediately, although the patient subsequently died from tuberculous meningitis. From 1889 to 1891, Wynter treated three more cases of tuberculous meningitis in the same fashion, all of them showing improvement for a while, although they subsequently succumbed to the disease.

Charles A. Morton (1891) followed the method outlined by Wynter. In discussing the pathology of tuberculous

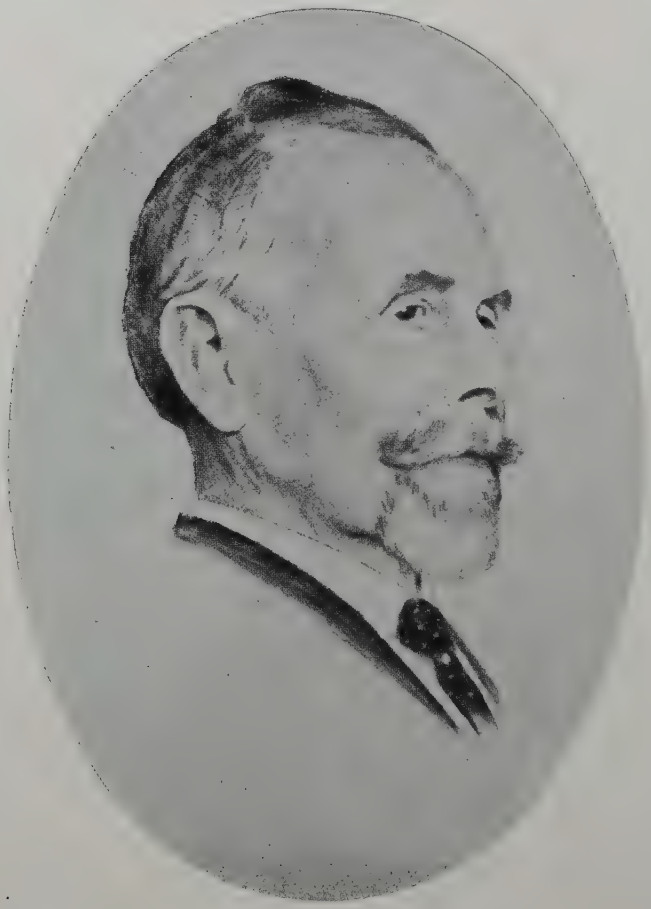

Fig. 4.—Heinrich Quincke (1842-1922).

meningitis with reference to its treatment by tapping the spinal subarachnoid space, Morton says:

"What symptoms can be relieved by it only the practice of the operation can show; that out of four cases operated on in the Middlesex Hospital in one there should have been contraction of the unduly dilated pupils, and in another slight improvement in the general condition, is encouraging when we remember that drainage was not maintained in all the cases. The operation does no harm and as the patient is already comatose, no anesthetic is required."

Morton, we see, tapped the patient when he was already in a comatose condition. Although he does not state definitely just what technic he employed, he does, at the beginning of his article speak of the recent procedure "of tapping the subarachnoid space of the spinal cord in cases of tuberculous meningitis." This would seem to indicate that he followed the method of Wynter; namely incision of the skin, introduction of a trocar between the vertebræ and the use of a continuous drain.

For the simplification and perfection of spinal puncture we must turn to Heinrich Quincke (1842-1922) (Fig. 4). Corning, who was the first to use spinal puncture, employed an operation that was fraught with danger to the cord, as the point at which he introduced the needle was too high up in the spinal canal. Wynter, it is true, did his puncture in the lumbar region, but his method necessitated the use of a large trocar, a continuous drain and a large incision in the skin. The procedure of Quincke was a vast improvement over those of his predecessors, both from the standpoint of simplicity and of safety. Quincke used only a plain needle and he so perfected the technic of spinal puncture that there is little that can be improved on his original method.

At the Tenth Congress for Internal Medicine, Quincke reported two cases of hydrocephalus treated by means of withdrawal of the cerebrospinal fluid. The first was one

of chronic hydrocephalus in which the fluid was removed by trephining and in which the contractures of the extremities and of the neck subsequently disappeared. The second was that of a child in which lumbar puncture resulted in great improvement. From these and similar observations Quincke concluded that spinal puncture for therapeutic purposes was indicated in marked cerebral pressure, especially in cases of tuberculous meningitis and

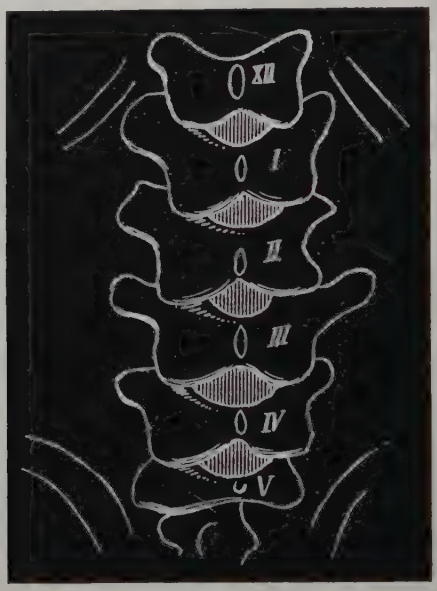

Fig. 5.—Drawing accompanying original article on lumbar puncture by Quincke, representing equal intervertebral spaces in lumbar region of skeleton of a one-year-old child.

acute hydrocephalus. Quincke not only described the technic of spinal puncture, but he also measured the pressure of the cerebrospinal fluid and determined its chemical composition so far as he was able with the chemical technic at his command. (Figs. 5 and 6.)

For two years after Quincke's experiments with spinal puncture no reports appeared in literature regarding its use. It was not until 1893 that Lichtheim called attention

to spinal puncture as a valuable aid in diagnosis, and two years later, in 1895, Fübringer reported 107 punctures in eighty cases. In America, Browning, in 1894, reported a series of spinal punctures and G. W. Jacoby, in 1895-6, reported 30 punctures. Since 1896 spinal puncture has been quite generally adopted as a routine procedure for diagnostic and therapeutic purposes.

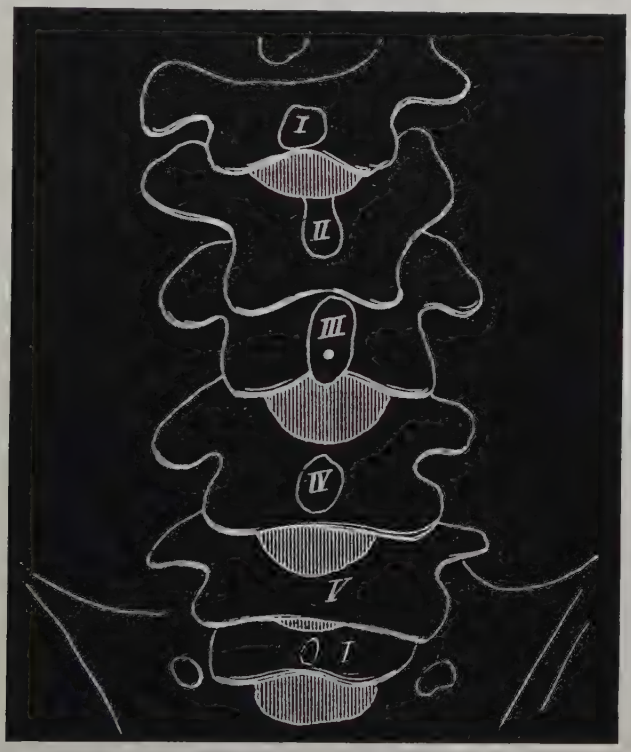

Fig. 6.—Drawing accompanying original article on lumbar puncture by Quincke, representing lumbar region of skeleton of a six-year-old child, showing the wide third intervertebral space.

That fluid could be removed from the ventricles was known to the ancients. As previously stated, Hippocrates was credited with tapping the ventricles in a case of hydrocephalus. There is no record, however, of his ever having performed this operation during life.

The tapping of the ventricles in the living was first done by Middeldorpf in 1856 (Fig. 7), who also first described the needle and instruments he used. Moss, in 1869, performed the first exploratory puncture of the brain. In

Albrecht Theodor Middeldorpf

Fig. 7.—Albrecht Middeldorpf (1824-1868)

1893, Schmidt independently described diagnostic puncture of the brain and ventricles and in 1896, Payr used this method for obtaining cerebrospinal fluid from dogs. Ventricular puncture as a therapeutic measure was used by

Quincke in 1888 in a case of hydrocephalus, by Robson in one of purulent meningitis, and by von Bergmann in 1889, who used it to relieve the symptoms by withdrawing fluid in a case of tuberculous meningitis. Kocher, in 1899, first used this route for the injection of medicaments, introducing antitetanic serum into the ventricles in a case of tetanus. Neisser and Pollack, in 1904, and Pfeiffer, in 1908, both improved the technic and used this method extensively. Cushing and Sladen, in 1908, first injected antimeningococcic serum into the ventricles in a case of obstructive hydrocephalus. Dandy, in 1918, was the first to inject air into the ventricles and then radiograph them for the diagnosis of intracranial neoplasms. Today, ventricular puncture in infants is considered a very useful method for obtaining cerebrospinal fluid.

Occipito-atlantoid drainage of the cisterna magna in man for therapeutic purposes has been done by Parker in 1893, Balance in 1897 and Cushing and Baynes in 1912 by means of an open operation. Cistern puncture, however, is a relatively recent method which has been mainly developed in this country. Quincke, in 1905, first suggested that cerebropsinal fluid might be obtained from the basal cisterns, but he considered the proceeding too impracticable and dangerous for routine use. In 1913, Dixon and Halliburton, in their work on the hormone of the chorioid plexus, inserted trocars through the occipito-atlantoid space in the dog, by means of which they studied the rate of flow of the fluid. This method of cistern puncture was perfected and used extensively in animals by Wood, in 1914. The first attempt to tap the cisterns in man with a needle was made by Bériel, in 1909, and later by Cazaman, in 1916, by inserting a needle below the eye anteriorly, using the sphenoidal route. However, it was not until 1919 that occipito-atlantoid puncture of the cisterna magna in man, by means of a needle, was first performed by Wegeforth Ayer and Essick. Since 1920, this method of obtaining

cerebrospinal fluid has been used extensively. Sicard, in 1923, was the first one to inject lipiodol into the cistern as a roentgenographic aid in the diagnosis of cord tumors.

MODERN RESEARCH ON CEREBROSPINAL FLUID

With methods available for obtaining cerebrospinal fluid, research into the nature of the fluid was given decided impetus. Next to the blood, cerebrospinal fluid has become an object of greatest study. All the new discoveries in medicine have been applied to the study of cerebrospinal fluid.

Bacteriology, serology, and chemistry have all played important rôles in shaping the history of cerebrospinal fluid. As for bacteriology, there is hardly a discovery in this field that does not bear a more or less direct relation to the history of cerebrospinal fluid. The discovery of the tubercle bacillus by Robert Koch (1882) changed the name of acute hydrocephalus to tuberculous meningitis, and the conception as to its nature accordingly. The discovery of the pneumococcus by Sternberg (1881) described more accurately by Fränkel (1885), the discovery of the influenza bacillus by Pfeiffer (1892) and the demonstration of trypanosome in cerebrospinal fluid by Castellani (1903) helped to establish the cause of many inflammatory processes of the meninges.

A special chapter was contributed to the history of cerebrospinal fluid by the discovery of the meningococcus. In 1885 Leichtenstern reported four cases of epidemic meningitis and demonstrated in the pial exudate of two of the cases that came to autopsy a "few round cocci of equal size, some appearing singly, others in small irregular groups similar to the arrangement of gonococci, usually intracellular but also extracellular." In a second communication Leichtenstern reported the cultural characteristics of the bacteria found postmortem in the meningeal exudate. They

were not, however, uniform. Some were short bacilli, others were long bacilli, and still others corresponded to what we now call meningococci.

Two years later (1887) Weichselbaum gave a full description of diplococci found in the direct smear of meningeal exudate observed postmortem in people who succumbed to meningitis (Fig. 8). His description of the cultural characteristics of these bacteria was so accurate that for many years very little more was added to our knowledge of meningococci. It is only in the last few years that additional knowledge has been obtained in connection with meningococci.

According to Bokay, Heubner (1896) was the first one to demonstrate meningococci in cerebrospinal fluid obtained from a living person.

Serology has added a great deal to the diagnostic and therapeutic uses of the cerebrospinal fluid. Bordet's discovery of complement fixation, Ehrlich's work on immunity and Wassermann's serologic test all found practical applications in the cerebrospinal fluid. However, probably the most beneficial contribution in the field of serology was the discovery of antimeningococcus serum by Jochmann in Germany and by Flexner in America and the introduction of the intraspinal injection of the serum by Flexner.

Chemistry, too, has had its share in shaping the history of the cerebrospinal fluid. Lassaigne determined the composition of cerebrospinal fluid for Magendie. Halliburton worked on the chemical composition of fluid from cases of rhinorrhea obtained by Sir St. Clair Thomson. Many other chemists and physiologists also worked on the nature of the cerebrospinal fluid.

Chemistry has not only taught us the composition of this, the clearest of body fluids, but has also shed light on the diagnosis of meningitis and other affections of the central nervous system.

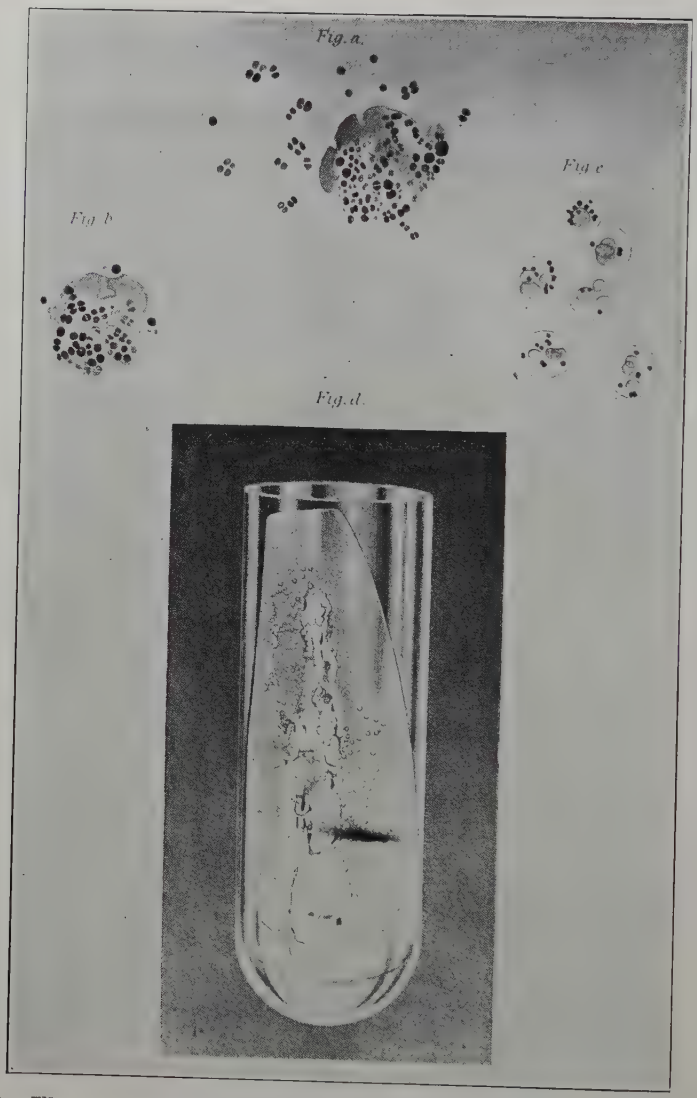

Fig. 8.—Illustration of meningococci in smear and in culture, accompanying original article of Weichselbaum in 1887.

Cytology advanced the study of cerebrospinal fluid to a great degree. Widal, Ravaut, and Sicard led the way in this phase of study, and they were followed by many workers on the subject.

Finally, the recent offspring of science, physical chemistry, is making its impress also on the history of cerebrospinal fluid. The study of the H-ion concentration, cataphoresis, the Lange colloidal gold test, the ninhydrin reaction and the precipitation tests, all of which are based on physicochemical principles, have thrown light on diseases of the central nervous system in general and on the composition of this body fluid in particular.

It would hardly be an exaggeration to say that the history of cerebrospinal fluid in many respects is but a miniature history of modern medicine.

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CHAPTER II

ANATOMY OF THE STRUCTURES ASSOCIATED WITH THE CEREBROSPINAL FLUID

The cerebrospinal fluid (subarachnoid fluid, liquor cerebrospinalis, liquide cephalorachidien, Zerebrospinalflüssigkeit) is contained in the ventricles of the brain and in the subarachnoid space of the brain and cord.

THE VENTRICLES

The ventricles of the brain are five in number, two lateral, third, fourth and fifth (Figs. 9 and 10).

Each one of the two lateral ventricles is located in the central part of the cerebral hemisphere and is divided into a central portion, an anterior or ascending, a posterior and an inferior or descending horn.

The central portion or the body of each ventricle lies in the region of the parietal lobe. The anterior horn passes from the body forward and outward into the frontal lobe. The posterior horn passes backward and outward into the occipital lobe. The inferior horn passes downward and outward into the temporal lobe. The two lateral ventricles are separated from each other by a thin triangular partition called the septum pellucidum. This partition forms the inner wall of the body of each ventricle. It also encloses the fifth ventricle.

The third ventricle is a narrow triangular cleft between the two thalami extending from the lamina terminalis anteriorly, to the aqueduct of Sylvius or the cerebral aqueduct posteriorly. It measures about an inch in length from before backward and a quarter of an inch in breadth at its widest part. It opens in front through the foramina of Monro (interventricular foramina) into the

lateral ventricles and is continuous behind with the upper end of the aqueduct of Sylvius connecting with the fourth ventricle.

The fourth ventricle, or the cavity of the hind brain, is a diamond-shaped space, continuous at its upper end with the aqueduct of Sylvius, and at its lower end with the central canal of the spinal cord. The upper part of the ventricle is located between the pons in front and the cerebellum behind. The lower part lies in the interior of the medulla.

The fifth ventricle is a cavity in the septum pellucidum, and is entirely separate from the other ventricles. It is bounded above and in front by the corpus callosum and below and behind by the body and anterior pillars of the fornix.

A layer of cubical ciliated epithelial cells, known as the ependyma, lines the lateral, third, fourth and fifth ventricles (Fig. 11). Whether the ependyma plays any rôle in the production of cerebrospinal fluid is a matter of conjecture.

THE CHORIOID PLEXUS

Lining the ventricles there is a tuft of blood vessels, covered by a single layer of epithelium called the choroid or chorioid plexus (Figs. 9, 10, and 11). This plexus is an ingrowth or folding of the pia, the layer of the meninges immediately adjacent to the brain. The average length of the chorioid plexus is 7 cm. Faivre has estimated the total area of the free surface of the chorioid plexus at 112 sq. cm. and Weed at twice that amount. The chorioid plexuses are largest in the embryonic state, becoming proportionately smaller after the sixth month of fetal life.

Two-thirds of the blood supply of the plexus in man is furnished by the anterior chorioid branch of the internal carotid artery which enters the plexus at the anterior end of the descending horn of the lateral ventricle. The re-

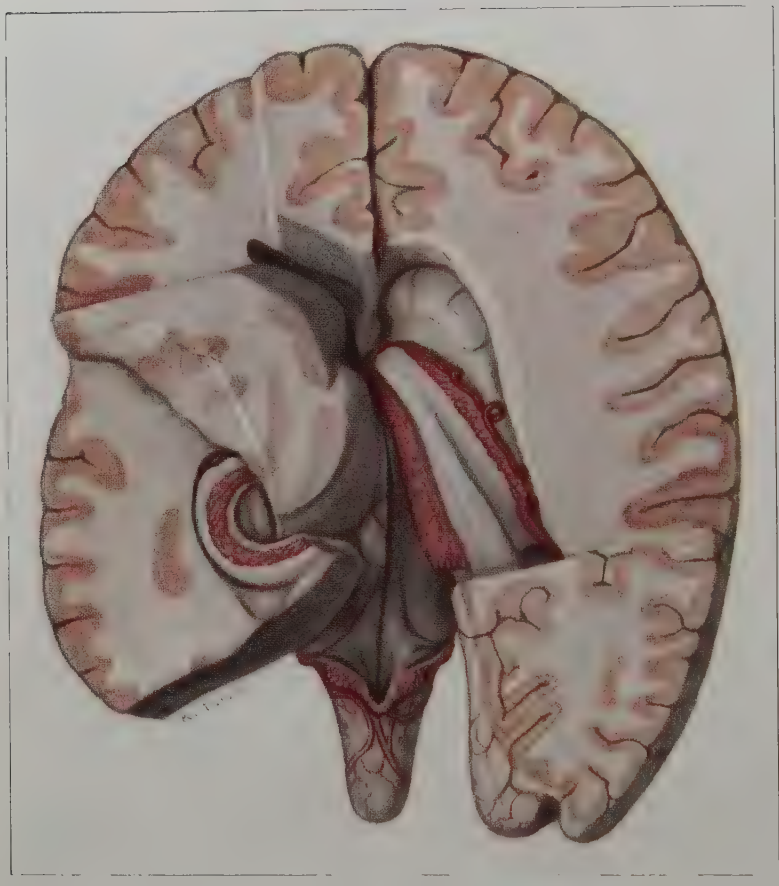

Fig. 9.—Section of human brain showing the chorioid plexus, the extent, relations, and intercommunications of the brain ventricles. (See Fig. 10.)

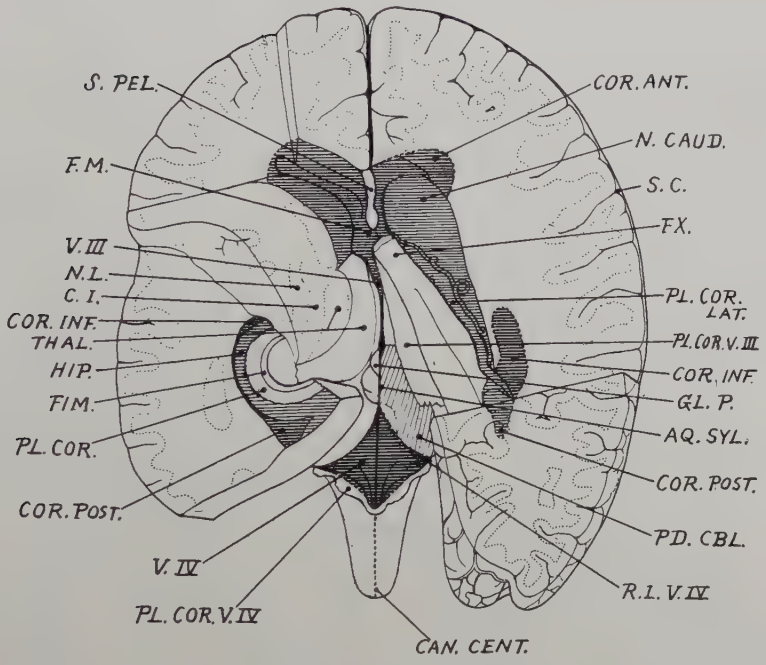

Fig. 10.—A diagram of Fig. 9. The verticles are shaded and outlined by solid lines. Those portions of the ventricle hidden from view are outlined by dotted lines.

S. PEL., Septum pellucidum.
F. M., Foramen of Monro.
V. III., Third ventricle.
N. L., Lentiform nucleus.
C. I., Internal capsule.
COR. INF., Inferior horn of lateral ventricle.
THAL., Optic thalamus.
HIP., Hippocampus.
FIM., Fimbria.
PL. COR., Lateral chorioid plexus.
COR. POST., Posterior horn of lateral ventricle.
V. IV., Fourth ventricle.
PL. COR. V. IV., Reflected chorioid plexus of fourth ventricle.
CAN. CENT., Position of central canal.
COR. ANT., Position of anterior horn of lateral ventricle.
N. CAUD., Caudate nucleus.
S. C., Fissure of Rolando (central sulcus).
FX., Fornix cut through at column of the fornix.
PL. COR., LAT., Lateral chorioid plexus.
PL. COR. V. III., Reflected chorioid plexus of third ventricle and septum interpositum.
COR. INF., Position of the inferior horn of lateral ventricle.
GL. P., Left half of pineal body.
AQ. SYL., Aqueduct of Sylvius.
COR. POST., Position of posterior horn of lateral ventricle.
PD. CBL., Cut surface of cerebellar peduncles.
R. L. V. IV., Lateral recess of fourth ventricle.

mainder is supplied by the posterolateral chorioid artery, a branch of the posterior cerebral. These arteries break up into arterioles, the largest of which are visible to the naked eye. After passing through the network of capillaries, the blood returns through the chorioid vein to the internal cerebral veins where it joins its fellow and forms the cerebral vein, or vein of Galen.

Fig. 11.—Photomicrograph of chorioid plexus. x140. The blood vessels are engorged. At the lower portion of the field the ependymal lining of the ventricle is shown.

The walls of the blood vessels of the chorioid plexus, measure, in some tufts, 0.2 mm. in thickness, while in others they form only a thin membrane between the lumen and the cuboidal cells on the surface. Much variation exists also in the size of the lumina.

Sundwall divides the vessels of the chorioid plexus into two groups: (1) The vessels with thick walls, which as a rule, possess narrow lumina and have the same general structure as the small arteries. Weigert's stain shows a well-developed internal elastic layer, which in most instances is corrugated. In the media, which is quite well developed, fine, wavy, elastic fibers may be seen. The fibers may be traced to the cuboidal cells for which they frequently form a basic membrane. (2) The second group of vessels are those with comparatively thin walls and wide lumina. These may be regarded as veins or sinuses. No muscular tissue can be made out in the walls of this second group, the walls being composed almost entirely of white fibrous connective tissue and are so similar throughout in their structure that they can not be differentiated into intima, media, and adventitia. Only here and there may be seen a few fine elastic fibers.

The walls contain numerous small vessels and capillaries (vasa vasorum) of varying caliber. They are rich also in nuclear elements, such as endothelial cells, connective-tissue cells and interstitial granule cells.

THE MENINGES

The meninges of the brain and cord consist of three layers: the dura mater, the arachnoid and the pia. These three layers are separated from each other by two spaces —the subarachnoid and the subdural.

The dura mater, or the outer layer of the meninges, is rough externally and smooth and shiny internally. It consists of a cranial and a cerebral portion. The cranial portion serves as internal periosteum for the cranial bones and is rich in blood vessels and nerves.

The inner layer of the dura mater is covered by the parietal layer of the arachnoid which in turn forms the outer boundary of the subdural space. Between the two layers of the dura are enclosed the large venous sinuses.

As the cranial nerves enter the foramina in their exit from the cranium, they receive a tubular prolongation of the dura, which accompanies the nerve trunk for a short distance. This prolongation, called the dural sheath, is separated from the nerve by the underlying subdural cleft, and finally becomes continuous with the epineurium, while the subdural space communicates with the lymph clefts within the connective tissue envelopes of the nerves.

The arachnoid or middle layer of the meninges is a delicate nonvascular connective tissue structure located between the dura externally and the pia internally. Over the summit of the cerebral convolutions the arachnoid and pia are so closely united that they constitute practically a single membrane. In other places, however, these layers are connected only by the trabecula of arachnoid tissue.

The pia mater covers the brain closely, dipping into the fissures and sulci and covering the convolutions.

It consists of five layers of tissue, an external and an internal layer of endothelium, which cover an external and internal elastic layer, the latter of which encloses a middle layer of connective tissue which contains pigment cells.

The cranial pia mater forms two triangular folds, the tela chorioidea superior and the tela chorioidea inferior.

THE SUBARACHNOID SPACES

The subarachnoid cavity or space is situated between the pia and arachnoid layers. This space is divided into numerous small intercommunicating cavities by trabeculae which pass from the pia to the arachnoid. Over the surface of the convexity of the brain where the pia and arachnoid layers are in close contact, this cavity is naturally very small. However, in the sulci between the gyri, triangular spaces are left in which the trabeculated arachnoid tissue is found, for the pia mater dips into the sulci, whereas the arachnoid bridges them from gyrus to gyrus.

At certain parts of the brain the subarachnoid space becomes especially large, and they are then called subarachnoid cisterns; in these, the trabeculation is less abundant.

The Cisterns

The cisterns, seven in number, are named according to their locations: the cisterna cerebello-medullaris, or cis-

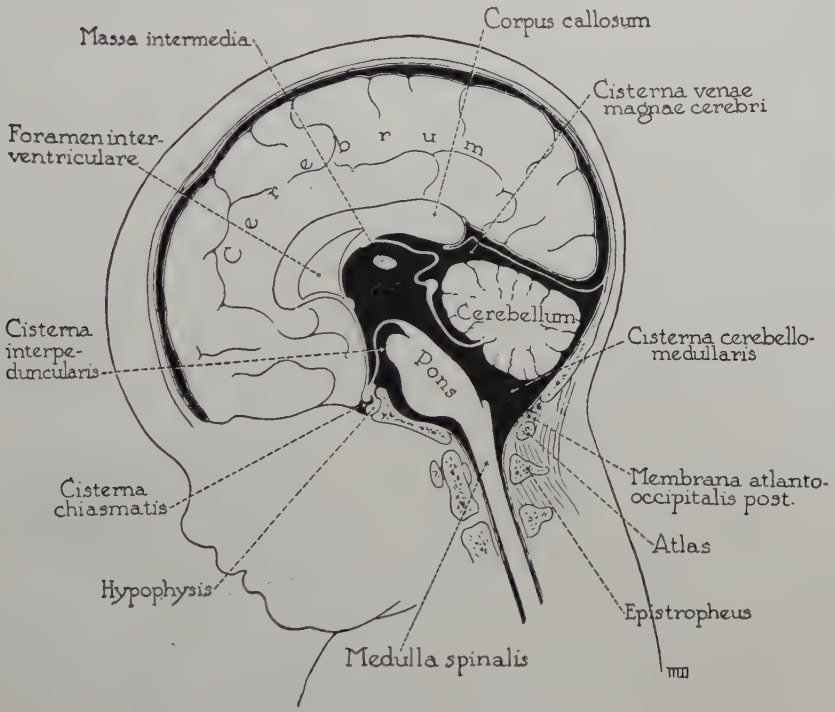

Fig. 12.—Showing various cisterns.

terna magna; cisterna pontis; cisterna interpeduncularis; cisterna chiasmaticus; cisterna venae magnae cerebri; and right and left cisternae fossae cerebri lateralis (Fig. 12). The largest and most important of these cisterns is the cisterna cerebello-medullaris, or cisterna magna, formed by the arachnoid bridging the wide interval between the in-

ferior surface of the cerebellum and the medulla. It is from this cistern that cerebrospinal fluid may be obtained from the living.

COMMUNICATIONS

The cerebrospinal fluid in one ventricle of the brain communicates directly with the fluid in the other ventricles through the various openings connecting them. The only exception to this rule is the fifth ventricle which contains very little or no fluid. Thus, the fluid in the lateral ventricles flows into the third through the foramina of Monro, and the fluid in the third communicates with that in the fourth by means of the aqueduct of Sylvius. (Figs. 9 and 10.)

The cerebrospinal fluid of the subarachnoid space communicates with the fluid in the ventricles of the brain through the foramen of Magendie which opens into the posterior part and the two foramina of Luschka which open into the lateral recesses of the fourth ventricle and through numerous other apertures which open into the lateral ventricles. Some authors, notably Schmorl, claim that no communication exists between the cerebrospinal fluid in the ventricles of the brain and the fluid in the subarachnoid spaces of the brain and cord. They base this claim on two observations: (1) the finding in cases of icterus of bile in the cerebrospinal fluid of the cord, but not in the fluid of the ventricles; (2) on the finding in certain cases of a positive Nonne-Apelt reaction in the cerebrospinal fluid of the cord and a negative reaction in the fluid of the ventricles.

The best evidence that a communication exists between the ventricles of the brain and the subarachnoid spaces is the commonly observed fact that in hemorrhage into the ventricles the fluid obtained by lumbar puncture contains blood. It is also well known that when a dye is injected into the ventricles, it can be recovered by

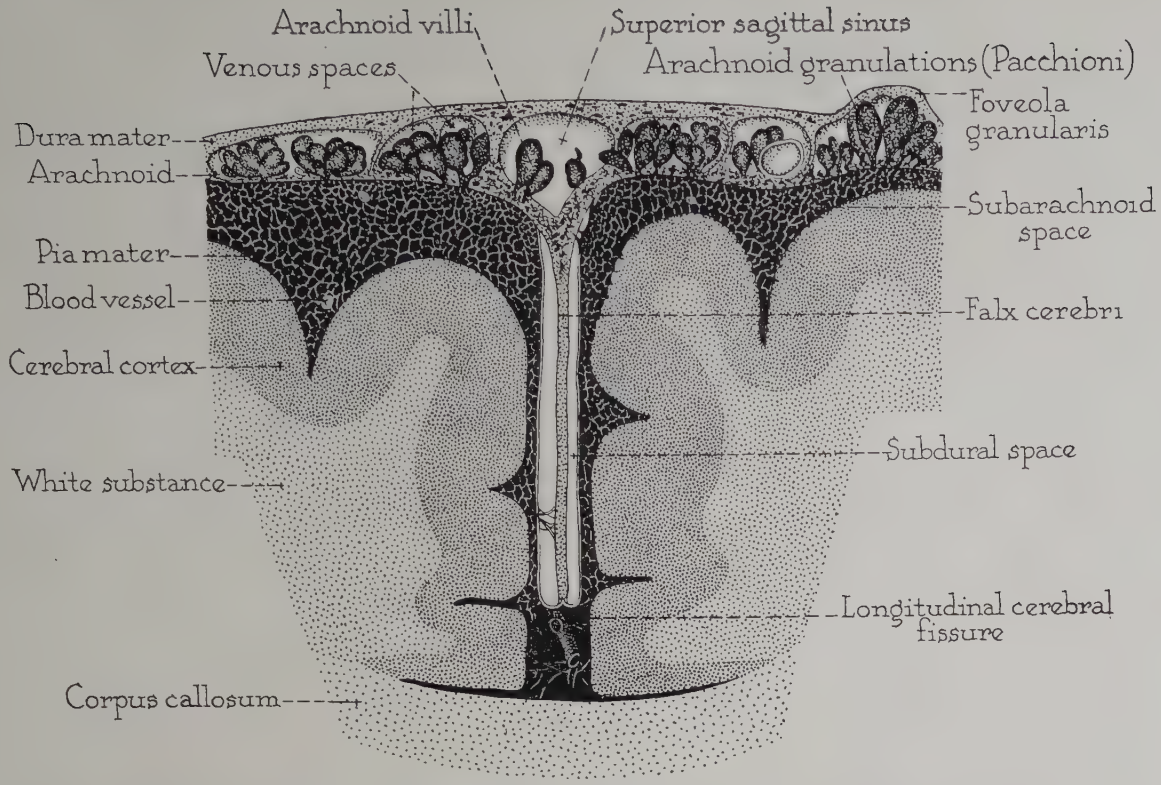

Fig. 13.—Frontal section of the meninges and brain showing arachnoid granulations (Pacchionian bodies). (After Key and Retzius.)

lumbar puncture in a few minutes. Vice versa, if the colored fluid is injected into the cisterna magna it can be recovered from the lateral ventricle. It is also well known that a tense fontanelle will go down with the withdrawal of cerebrospinal fluid by lumbar puncture. All this points to a direct communication between the ventricles of the brain and the subarachnoid space.

PACCHIONIAN BODIES

The Pacchionian bodies, or arachnoid granulations, or arachnoid villi are clusters of grayish red elevations, each one of which varies in size from that of a millet seed to that of a grain of wheat. They penetrate the dura mater and project into the sinuses or into the venous spaces. They are most numerous and largest in the vicinity of the superior sagittal sinus. They are present in smaller numbers in the region of the temporal lobe, on the cerebellar surface of the transverse sinus, straight sinus, and superior petrosal sinus.

The Pacchionian bodies often become so large that they push up the dura mater and produce depressions on the inner wall of the overlying bone, causing the so-called foveola granularis Pacchioni (Fig. 13).

The arachnoid villi, according to some authors, are rarely seen before the third year of life, and usually appear only after the seventh and sometimes only after the tenth year of life. They usually increase in size and number as age advances, and are less developed in the female than in the male. Weed, however, found microscopic evidence of arachnoid villi even in infants.

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CHAPTER III

PHYSIOLOGY OF THE CEREBROSPINAL FLUID

RATE OF FORMATION

The rate of formation of cerebrospinal fluid is still a matter of conjecture. Falkenheim and Naunyn observed that from 1 c.c. in six minutes to 1 c.c. in forty minutes flowed out of a cannula introduced into the subarachnoid space of a dog. In another dog, weighing 23 kilos, they observed as large a flow as 240 c.c. of fluid in twenty-four hours and in still another dog, weighing 20 kilos, they reported a flow of 36 c.c. in twenty-four hours. According to their experiments there does not seem to be any relation between body weight and the rate of formation of cerebrospinal fluid nor between the rate of formation and the arterial pressure. In the numerous reports of cases of cerebrospinal rhinorrhea, the amount of fluid flowing out from the nose varied from 96 c.c. to 720 c.c. per day. Tillaux, for instance, reports a case in which there was a communication between the subarachnoid space and the dura and in which the daily flow of cerebrospinal fluid from the nose averaged one-fourth of a liter. Wallace MacKenzie reports a case of cerebrospinal rhinorrhea where the average flow of fluid per hour was one ounce, making a total of 720 c.c. in a day. In trauma of the spinal column even greater amounts of fluid have been observed, as in the case of Giss in which there was a flow of fluid measuring from one and one-half to two liters. It seems likely, however, that the large amounts of cerebrospinal fluid observed in cases of trauma are no indication of the normal rate of formation of cerebrospinal fluid, as it is well known that whenever there is irritation of a serous membrane there is an increase of the fluid in the cavity.

So far as we know, no one has as yet determined the rate of formation of cerebrospinal fluid under normal conditions.

CIRCULATION

That the cerebrospinal fluid has a circulation has been shown by Magendie, but the mode of circulation has not been entirely established. Dyes injected into the ventricles can be detected in the fluid obtained by lumbar puncture within a few minutes. Kramer, in 1912, showed that when methylene blue is injected into the lumbar portion of the subarachnoid cavity of a dog and the animal is killed ten to twenty minutes later, the stain is found over a varying distance of the surface of the spinal cord, at times all the way to the medulla, at other times not so far. The floor of the fourth ventricle, however, is stained with methylene blue as are the cerebellum, the aqueduct, the entire ventricular system of the brain, the subarachnoid space at the base of the brain, as well as the sheaths of the cranial nerves. Blackfan and Dandy injected phenolsulphonephthalein intraspinally and were able to demonstrate the dye a few minutes later in the ventricles of the brain. This shows that there is not only a circulation of the cerebrospinal fluid downward but also upward toward the ventricles. It is thought that the fluid is formed in the ventricles of the brain, that it passes through the foramina of Magendie and Luschka into the subarachnoid space of the brain, then upward along the convexity of the brain and also downward along the posterior aspect of the spinal cord. On reaching the end of the cord the fluid passes upward along the anterior surface of the cord. Some of the fluid is absorbed there. The rest spreads over the convexities of the hemispheres whence it is absorbed.

RATE OF ABSORPTION

The data on the rate of absorption of the cerebrospinal fluid are not numerous. Duret was able to introduce 583 c.c. of water into the subarachnoid space of a dog in the

course of two hours. Naunyn and Schreiber introduced 400 c.c. of physiologic salt solution into the subarachnoid space of a dog, weighing 9½ kilograms, in the course of an hour and three quarters, using 100 mm. mercury pressure for the injection. Falkenheim and Naunyn showed that the absorption is rapid even when the fluid is injected with very little force. Dandy and Blackfan injected 1 c.c. of phenolsulphonephthalein into the subarachnoid space of a dog after withdrawing 1 c.c. of cerebrospinal fluid. They examined the quantity of phenolsulphonephthalein excreted in the urine by a colorimetric method, and found that in the first hour after the injection there were 16.6 per cent of phenolsulphonephthalein excreted in the urine; in the second, 17.8 per cent; in the third, 13.6; in the fourth, 7.2 per cent; in the fifth, 4.5 per cent; in the sixth, 2.2 per cent; in the seventh, 1.3 per cent; and in the eighth, 1.3 per cent. From these experiments they concluded that the absorption of the cerebrospinal fluid is fairly regular for a period of from three to four hours, and that it diminishes progressively after this time. They estimate that in a minimum of four to six hours, the total quantity of cerebrospinal fluid present at any one time is absorbed, making necessary a complete renewal of the cerebrospinal fluid in the system four to six times a day.

The above, however, can not be taken as an index for the rate of absorption of the cerebrospinal fluid, as phenolsulphonephthalein is a foreign substance, and, as is well known, a foreign substance is rapidly eliminated from the body, without reference to the absorption power of the body fluids. One, for instance, is not justified in saying that since 60 per cent of a dye is excreted in the urine in two hours by the kidney, 60 per cent of the water of the blood is excreted in two hours. Foreign substances are eliminated by a special mechanism and bear no relation to the absorption of the body fluids.

So far the rate of absorption of cerebrospinal fluid has not been determined, and I believe will not be deter-

mined so long as the rate of formation of the fluid is not known, for the rate of absorption naturally depends on the rate of formation.

CHANNELS OF ABSORPTION

Quincke was able to trace cinnabar, injected into the subarachnoid space, along the sheaths of the upper spinal nerves, along the sheaths of the optic nerves as far as the episcleral space of Schwalbe, and in the Pacchionian granulations. He could find no cinnabar granulations in the visceral organs or in the general circulation. Halliburton and Dixon found that dyes injected into the cerebrospinal fluid travel along the sheaths of the cranial nerves, especially the olfactory. Mott considers the perivascular lymphatics as the channel of absorption. It has been proved by others, also, that a portion of the fluid is drained by the lymphatics into the deep cervical glands, and that a small portion flows into the lymph vessels of the nose, the perilymph spaces of the labyrinth of the ear and into the perineural sheaths. This is somewhat substantiated by the cases of cerebrospinal rhinorrhea reported in the literature. It has been found, however, that normally the absorption by way of the lymphatic system removes only a very small quantity of the fluid. Hill, Ziegler, and Spina showed that methylene blue injected into the subarachnoid space can be recovered from the stomach in twenty minutes, while it takes hours before the lymphatics of the neck are discolored by the stain. Dandy and Blackfan introduced a cannula into the thoracic duct after they had injected phenolsulphonephthalein into the subarachnoid space and found that there was very little absorption by the lymph, compared with that by the blood.

These and many other experiments indicate that the greatest amount of cerebrospinal fluid is absorbed into the blood stream proper.

Key and Retzius, as far back as 1875, described in their masterly monograph, the structure of the Pacchionian

granulations in the walls of the cerebral veins and sinuses. They believed that the cerebrospinal fluid is absorbed from the subarachnoid space by means of these granulations.

Since the work of Key and Retzius, cerebrospinal fluid absorption has been the subject of many controversies and to this day has not been settled. One of the reasons the Pacchionian bodies have not been considered the main or only channel of absorption is the generally accepted opinion of anatomists that these bodies are absent in infancy and in lower animals, which if true, could not be reconciled with the idea of cerebrospinal fluid absorption.

Recently, however, Weed found microscopic evidence of the Pacchionian bodies or as he calls them, arachnoid villi in infants.

Most authors now agree with Weed that the fluid is absorbed by way of the arachnoid villi and that the villi transmit cerebrospinal fluid from the subarachnoid space into the cerebral sinuses by a process of filtration from a point of higher to a point of lower pressure.

PERMEABILITY

It is conceded by most observers that under normal conditions no foreign substances, or at least very few, pass from the blood into the cerebrospinal fluid. This resistance of the meninges to the entrance of a foreign substance is held to be due to the impermeability of the meninges, although, if we accept the view that the cerebrospinal fluid is secreted by the chorioid plexus we should speak rather of the impermeability of the chorioid plexus. Various experiments have been made to demonstrate this property of the chorioid.

Cavazzani injected potassium iodide into dogs intraperitoneally and recovered only very small amounts of it in the cerebrospinal fluid. Sicard, Lewandowsky, and Rotky repeated the experiment and could not detect potassium iodide in the cerebrospinal fluid at all. Lewandowsky found that a few centigrams of sodium ferrocyanide in-

jected into the subarachnoid space rapidly produced toxic symptoms while four to six grams injected into the jugular vein in rabbits of the same weight produced no specific symptoms. These toxic effects could not have been attributed to the solution employed, for a 10 per cent salt solution injected into the subarachnoid space produced only slight effects. Lewandowsky was also able to show the transmissibility of very small traces of strychnine in the cerebrospinal fluid of lower animals, but none in man. Von Jaksch and Sicard could not detect the presence of mercuric salts after inunction into the skin. Livon and Bernard could detect salicylates, but in very small amounts, in the cerebrospinal fluid of a dog after intravenous injection. Loberg found that salicylic acid passed into the cerebrospinal fluid in small but constant amounts, the amount varying with the concentration of salicylic acid in the blood.

Mestrezat found that when sodium nitrate is administered to a normal individual before a spinal puncture is made, the fluid shows very little or no nitrate. Likewise the normal meninges are impermeable to uranin.

There are a few chemical substances, however, that do seem to be transmitted from the blood into the cerebrospinal fluid, namely hexamethylenamine, alcohol, urethane, and chloroform. Hexamethylenamine has been shown by Crowe, Hold and Ratsky to be present in the cerebrospinal fluid of both man and animal after administration of the drug by mouth. This observation has led to the suggestion of giving hexamethylenamine by mouth in meningitis and poliomyelitis, but since the hexamethylenamine is present in the fluid in its original form and is not converted into formaldehyde, this suggestion has been abandoned. Alcohol was shown by Schottmüller and Schumm to accumulate in the cerebrospinal fluid in even larger amounts than in the blood. Bogen found equal amounts of alcohol in blood, urine, and cerebrospinal fluid.

Antitoxin passes over into the cerebrospinal fluid only in traces. The same is true of certain toxins. Behring injected hens both subcutaneously and intravenously with tetanus toxin and found that they suffered no ill effects. However, when he injected the same amount of toxin into the subdural space the hens died from typical tetanus.

Acetone, acetoacetic acid, lactic acid and bile have been found to pass over into the cerebrospinal fluid, even when the meninges are not affected. The chlorides in the fluid are increased in some cases of nephritis and the sugar is increased in diabetes.

I have shown that the ingestion or intravenous administration of glucose causes a rise in the sugar content of the cerebrospinal fluid even in normal conditions. In most cases studied, the greatest increase was between two to three hours after the injection of glucose both in meningitic and in nonmeningitic cases. In some cases, however, there was either no increase in the sugar or the maximum sugar curve was reached before the three hour period was up. The finding of Kelley that under the normal conditions the percentage of sugar in the cerebrospinal fluid is not changed by the intravenous injection of glucose, is not borne out by my work.

Arsenic does not permeate the normal meninges except in traces. Lead and mercury do not permeate them at all.

Parasites have been found to pass over into the fluid. Castellani demonstrated trypanosomes in the fluid in cases of sleeping sickness. Van Cott and Lutz, Bloch and others found trichina in the fluid of patients suffering from trichiniasis.

Some of the experiments on the impermeability of the meninges and chorioid plexus are not entirely convincing because they deal with negative evidence. Very frequently also the technic and method have been at fault. It is certain, however, that there is a vast difference between the transmissibility of chemical and immune substances in health and in disease. Although we may not

know positively whether the meninges or chorioid plexus are entirely impermeable in health, we do know that they become permeable in disease—a fact of great importance in the genesis and also in the diagnosis and treatment of the diseases of the meninges (Table I).

TABLE I

MENINGEAL PERMEABILITY

	Substances normally in blood and cerebrospinal fluid	Substances normally not in blood and cerebrospinal fluid
Substances to which the permeability is almost complete	Chlorides; magnesium; sodium; carbon dioxide	Alcohol
Substances to which the permeability is partial	Protein; glucose; calcium; potassium; iron; sulphates; creatinine; uric acid; acetone; lipase; diastase; amino acids; inorganic phosphates; lactic acid; urea	Chloroform; urethane; hexamethylenamine
Substances to which permeability is minute or absent	Cholesterol; fibrinogen; bilirubin; most ferments and immunologic substances	Arsenic; lead; mercury; bromides; iodides; uranin; toxins; nitrates; salicylates; strychnine

FUNCTION

That the cerebrospinal fluid has a mechanic function there is no doubt. The fluid forms a water bed around the cord and brain and thus prevents the jarring from external trauma. The fluid also equalizes the pressure between the brain and the cord. Magendie, many years ago, pointed out the following:

"The cerebrospinal fluid which is barely mentioned in the classical works, not only fills out the empty spaces in the skull and spinal canal, but has a greater function, namely, to exert a continual and regulated pressure on the neuron masses."

However, a number of other functions are ascribed to cerebrospinal fluid. Mott believes that it is the function of the fluid to give up carbon dioxide and water to the blood

and to take up oxygen and sugar. Cushing, and later Frazier, suggested that the fluid may be the medium of distribution of the active principle of the pituitary to the tissues of the central nervous system, which is essential to metabolism. Halliburton considers the fluid as a Locke modification of Ringer's solution. The sugar, as in Locke's solution, serves to supply the energy, the protein serves to repair the wear and tear resulting from the action of the nervous system, and the fluid as a whole acts as an ideal, physiologic salt solution bathing the neurones and maintaining their osmotic equilibrium.

According to Gaskel the neural tube is a primitive digestive canal, and the cerebrospinal fluid may therefore be considered a primitive gastric juice. Dandy calls attention to the gill-like appearance of the chorioid plexus which in turn inclines him to believe that the chorioid plexus and the cerebrospinal fluid are concerned in respiration. Pettit and Girard hold that the fluid has an internal secretion. Kafka holds that the cerebrospinal fluid contains ferments which serve as a protection against infection. Hassin believes that the function of the cerebrospinal fluid is to remove the waste products of the brain. The finding by Cavazzanni of the presence in the morning of a greater amount of solids in the cerebrospinal fluid than in the evening, may be interpreted by this theory to mean that during sleep the accumulated waste products of the brain are excreted into the cerebrospinal fluid.

Of the various theories advanced in regard to the function of the cerebrospinal fluid, that of mechanic function has an unquestionable basis. All the other theories are either open to objection of one kind or another, or lack in sufficient evidence, although it seems that the cerebrospinal fluid has more than a mere protective function, otherwise why its peculiar chemical composition? Mott's theory that the cerebrospinal fluid gives up CO_2 and water to the blood, and Cushing's and Frazier's suggestion that the fluid distributes pituitary substance to the central nervous system

need further confirmatory evidence. The theories of Dandy and of Gaskel do not appear at all plausible. As to the theory that the fluid destroys toxin, the objection may be raised that very few toxins are able to get into the cerebrospinal canal under normal conditions, as shown in the discussion on permeability. Hassin's theory of the excretory nature of the fluid does not seem probable, for we should expect to find more evidences of meningeal involvement in encephalitis, for according to his theory, the meninges absorb the waste products of the brain. Actually there is only little meningeal involvement in encephalitis. Halliburton's theory seems plausible, but needs confirmation. The large amount of salt, and the fairly large amount of dextrose in cerebrospinal fluid would make one think of cerebrospinal fluid as a modified Locke's solution bathing the nervous system. The carbonate content of the cerebrospinal fluid would make one think of cerebrospinal fluid as having not only the function of bathing the nervous system, but also as having as a part of its work the regulation of the alkali reserve of the nervous system. Whatever other function the cerebrospinal fluid may possess, it has a mechanical function in that it equalizes the pressure in the subarachnoid space and the ventricles of the brain.

ORIGIN

The question of the origin of cerebrospinal fluid is one that has engaged the attention of many physiologists and chemists, and even today the problem is far from settled, although attempts have been made to solve it through the aid of histology, chemistry, physiology, and pathology.

Carl Schmidt (1850) was the first to voice the opinion that cerebrospinal fluid was a secretion and not a transudate by virtue of the difference in the chemical composition of the blood and the fluid. Faivre (1854) also spoke of the intimate relation between the fluid and the chorioid plexus. Luschka (quoted from Meek) in 1855 published an impor-

tant monograph in which he produced evidence to show that cerebrospinal fluid must be considered as a secretion of the membranes of the brain. Jolly (1871) believed that "cerebrospinal fluid is a blood derivative and it is beyond doubt partly a result of transudation from the surrounding blood vessels and partly from the lymph spaces surrounding the blood vessels in the brain."

Luschka, Schlaepfer, Yoshimura, Ernst, Kafka, Mott and Meek found the existence of vacuoles in the chorioid plexus, and all, with the exception of Meek, connected the globules with the secretion of cerebrospinal fluid. Mott examined the chorioid plexus of human beings soon after death and, on staining with methylene blue, he found the cells of the chorioid plexus to contain many vacuoles. This, he believed, proved conclusively that the chorioid cells secreted some substance. He compared the epithelial cells of the chorioid with those of the lacrymal glands.

Physiologic evidence as to the secretion of the chorioid plexus was also brought forth by many observers. Kafka found that, after an injection of pilocarpine, the epithelial globules of the chorioid plexus were multiplied. Cavazzani in 1893 advanced negative evidence by showing that lymphagogues did not affect the cerebrospinal fluid. His observation that the alkalinity of cerebrospinal fluid was considerably less than that of the blood also led him to the conclusion that cerebrospinal fluid was a secretion. Cappelleti in 1901 came to the same conclusion regarding the origin of the cerebrospinal fluid. He found that ethyl ether and pilocarpine increased the flow of the fluid, whereas atropin and hyoscyamin retarded the flow. Pettit and Girard went a step further by showing that the cytoplasm of the chorioidal epithelium was doubled in amount following the injection of pilocarpine, muscarine or ether. Dixon and Halliburton brought about an increase in the flow of the fluid by injecting chorioid extract intravenously. They claim that the chorioid plexus contains a hormone

which, when liberated into the blood, becomes the precursor and regulating medium of the secretory activity of the plexus.

Interesting contributions to the chemical phase of the problem have been made by Schmidt, Polányi, Schottmüller and Schumm. The work of Schmidt has been mentioned. Polányi concluded, from the small protein content and the high molecular concentration of fluid in cases of hydrocephalus, that the fluid is not a transudate. Schottmüller and Schumm claimed that the fluid is not subordinate to the blood, as they had found the fluid in some cases to contain alcohol in as great and greater quantities than the blood. Leopold and Bernhard subscribe to the view of Cushing that the cerebrospinal fluid is secreted by the chorioid plexus on the ground that they were unable to find uric acid in the fluid of normal individuals.

Evidence from pathologic conditions, as to the secretive powers of the chorioid plexus has been furnished by other observers. Charles and Levy report a case of hydrocephalus in which there was hypertrophy of the chorioid plexus. Dandy and Blackfan occluded the aqueduct of Sylvius by a gelatine capsule and produced thereby an internal hydrocephalus. This would tend to show that the fluid is secreted above the aqueduct and most likely by the chorioid plexus. Cushing observed a clear transparent fluid exuding from the chorioid plexus in a case where the plexus was exposed during an operation. That part of the fluid might come from the ventricles themselves the work of Francini would indicate, as he noticed secretory phenomena of the ependyma cells of the ventricles after ether and pilocarpine injections.

It has been suggested by Mott and Cushing that there is a dual origin of the fluid, part of it coming from the chorioid plexus and part from the meninges. They base this assumption upon the presence of more cells and a greater quantity of protein in subarachnoid than in ventricular fluid. The inference is that the fluid which is se-

creted in the ventricles has added to it additional secretory or excretory products as it passes through the subarachnoid spaces. The formation of meningeal cysts following traumatic conditions of the meninges is further evidence that fluid may be formed in the meninges proper.

Comparative anatomy too has been drawn upon for evidence that the chorioid plexus is connected with the secretion of cerebrospinal fluid. It has been noted that the size of the chorioid plexus is in direct ratio to the size of the lumen of the ventricles. In urodeles that have large ventricles, the plexus is strongly developed, while in anures that have no ventricles the plexus is small.

On the other hand, there are observations that would tend to show that cerebrospinal fluid is not a secretion. Mestrezat, on the basis of chemical analysis of the blood plasma and the cerebrospinal fluid, concluded that the fluid is not a filtrate, a transudate, or a secretion, but a dialysate of blood plasma produced by a passage through special epithelial cells. McClendon, on physico-chemical grounds, claimed that the cerebrospinal fluid is an ultrafiltrate. Lewandowsky considered cerebrospinal fluid a lymph secretion. Arguments against the origin of the cerebrospinal fluid from the chorioid plexus are brought forth by Hassin on the basis of his histopathologic studies of the central nervous system. In degenerative conditions of the brain and cord, such as in subacute cord degeneration, multiple sclerosis, softening or abscess of the brain or cord, Hassin found the subarachnoid space and the chorioid plexus to contain lipoid substances. In cerebral hemorrhage he found blood pigments in the subarachnoid spaces, and in so-called solitary tubercles of the spinal cord, he found the subarachnoid to contain miliary tubercles. These findings, he believes, tend to show that the cerebrospinal fluid originates in the brain or spinal cord tissue, that it flows towards the ventricles and the subarachnoid space, that it carries with it the waste products of the central nervous

system, and that it is ultimately absorbed by the arachnoid villi as well as the chorioid plexus. The function of the chorioid plexus is, therefore, the absorption and not the secretion of the cerebrospinal fluid, Hassin believes.

From the various data presented, one would be inclined to believe that the chorioid plexus is located in the ventricles for some purpose, and possibly for the secretion of the cerebrospinal fluid. Yet the evidence brought forward to prove this point is not altogether convincing.

Mott's observation of the existence of vacuoles in the chorioid plexus, an observation that has been corroborated by Luschka, Findlay and Galeotti, does not necessarily indicate that the chorioid plexus secretes cerebrospinal fluid. Meek believes that the vacuoles are due to the melting of the fat in the epithelial cells of the chorioid through the action of such hardening fluids as alcohol and xylol, for chorioid cells which have not been subjected to alcohol and xylol do not show vacuoles. Pettit and Girard believe that these vacuoles are due to mechanical injury and to postmortem changes. Becht argues that secreting cells should not show vacuoles at all, but should be smaller than ordinary cells. He points out the fact that secreting cells in the parotid and other glands become smaller during the period of activity, whereas those of the chorioid plexus become larger. He notes other differences as well. While, in most glands, during the period of activity the cytoplasm is differentiated into an inner granular layer and an outer clear zone with well-defined nuclei, in the chorioid plexus, during activity, the very opposite takes place. The cytoplasm becomes differentiated into an inner clear and an outer granular zone and the nucleus can hardly be distinguished from the nucleus of the resting cells.

Cavazzani's evidence regarding the alkalinity of the cerebrospinal fluid does not hold good, because the methods used for the determination of the reaction were not the proper ones, and with newer methods, the reaction of the

fluid is found to be the same as that of the blood. As for the effect of pilocarpine in increasing the amount of cerebrospinal fluid, this does not necessarily show that the fluid is a secretion. The increase in the amount can just as readily be attributed to the action of the drug on the blood vessels. The effect of atropine in retarding the flow of cerebrospinal fluid would be significant if we were sure that atropine acts directly on the secreting cell.

As for the chemical evidence brought forth by Polányi, is it not plausible to assume that the cerebrospinal fluid may come from the blood, and that the smaller content of protein in the fluid be due to the changes the fluid undergoes during the process of filtration? Schottmüller's observation that there may be a greater amount of alcohol in the cerebrospinal fluid than in the blood may be explained on the ground of slower absorption from the cerebrospinal canal than from the blood, permitting the concentration to remain high in the cerebrospinal canal after most of the alcohol has made its escape from the blood through one of the organs of excretion. Moreover, the observation that the pressure of the cerebrospinal fluid varies directly as arterial and venous pressure, speaks for the filtration theory. Opposed to this, however, is the fact that cerebrospinal fluid pressure may also vary independently of arterial or venous pressure.

Until it is possible to remove the chorioid we shall not know conclusively whether the chorioid is the seat of the secretion of the cerebrospinal fluid. All that we can say at present with any degree of certainty is that there is proof to show that the cerebrospinal fluid is produced above the aqueduct of Sylvius.

The fact that nearly all constituents of the blood are present in the cerebrospinal fluid, and that the physicochemical properties of the cerebrospinal fluid are practically the same as that of the blood, would make one believe that the cerebrospinal fluid is a direct product of the blood.

The data presented in this chapter may be summarized in the following points:

1. The cerebrospinal fluid has a circulation.

2. The rate of formation of normal fluid is unknown. Likewise is the rate of absorption.

3. Absorption seemingly takes place by a process of diffusion from the subarachnoid space of the brain and of the cord, most likely by way of the Pacchionian bodies. Some absorption also takes place by the lymphatics draining into the deep cervical glands, into the lymph vessels of the nose, perilymph spaces of the labyrinth and into the perineural sheaths of the cranial nerves.

4. The meninges and the chorioid plexus, are not permeable, or very little so, under normal conditions.

5. The fluid exerts a mechanical function in that it equalizes the cerebrospinal pressure. The numerous other functions attributed to the fluid need further substantiation.

6. The origin of cerebrospinal fluid is unknown. There is some evidence pointing toward the theory that the chorioid plexus is the seat of origin of the fluid. There is also evidence pointing to the assumption that the fluid is a direct product of the blood or of the brain tissue.

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CHAPTER IV

NORMAL CEREBROSPINAL FLUID. PRESSURE

Observations by various workers on the pressure of cerebrospinal fluid under normal conditions have differed considerably. Magendie knew that the pressure of the cerebrospinal fluid was positive. Falkenheim and Naunyn claimed that it is necessary for the maintenance of the blood circulation of the brain that the cerebrospinal fluid remain at a certain pressure and they estimated the pressure under normal conditions to vary between 50 and 200 mm. of water (3.5 to 15 mm. of mercury) for a child one month to one year of age, with a correspondingly higher pressure for an adult. Quincke gave 40 to 60 mm. of water (3 to 4.5 mm. of mercury) as the normal pressure for children, and 150 (11 mm. of mercury) for adults; Adamkiewicz gave 80 to 100 mm. of water (6 to 7.5 mm. of mercury), and Sicard gave 200 (15 mm. of mercury) as the normal pressure. These differences may be attributed to the variations in technic, instruments and conditions with which these investigators worked. In general, the factors influencing the pressure of the cerebrospinal fluid may be classified under the following headings:

The type of apparatus used.

The position of the needle in the canal.

The amount of fluid withdrawn before the manometer is attached.

The age of the patient.

The position of the patient.

The site of puncture.

Intracranial arterial and venous pressure.

Rate of formation and of absorption of cerebrospinal fluid.

The brain volume.

TYPE OF APPARATUS

The fact that so many different manometers for measuring cerebrospinal fluid pressure have been described, indicates that there is yet no single apparatus that completely answers the purpose. The cerebrospinal fluid manometers may be grouped into four classes:

(a) Simple upright tube attached to the needle, into which the cerebrospinal fluid flows, and the height to which it rises, is measured. Such a manometer was used by Quincke in his original observations (Fig. 14), and is still

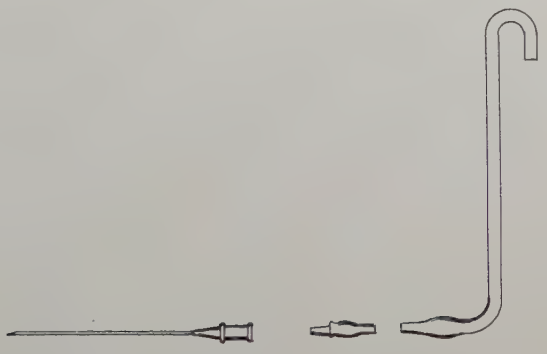

Fig. 14.—Apparatus of Quincke.

used by Ayer, Krönig (Fig. 15), and Fleischmann (Fig. 16). Quincke used an ordinary glass tube with a one-millimeter bore bent at the top, and an ordinary tape to measure the pressure. An arrangement like the one used by Quincke may be made at any laboratory by taking heavy glass tubing of one-millimeter bore, bending it at right angles below, and connecting it with hard rubber of one-millimeter bore to a tip fitting into an ordinary spinal puncture needle. The point to which the fluid reaches can be marked off and the height can then be measured on a slide or with a tape measure (Fig. 17). I used this arrangement for some time, but although it is of value, it is not accurate enough. The disadvantage of the Quincke apparatus lies in the fact that it

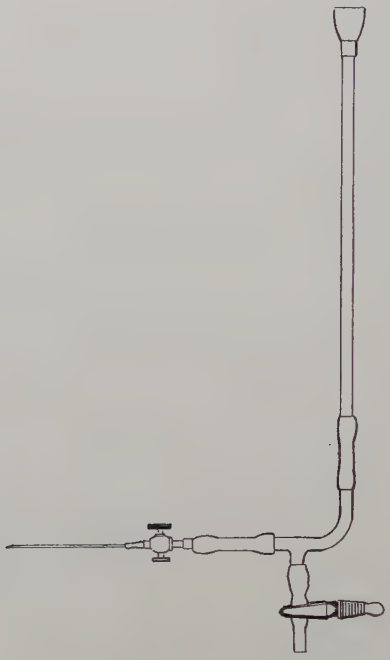

Fig. 15.—Apparatus of Krönig.

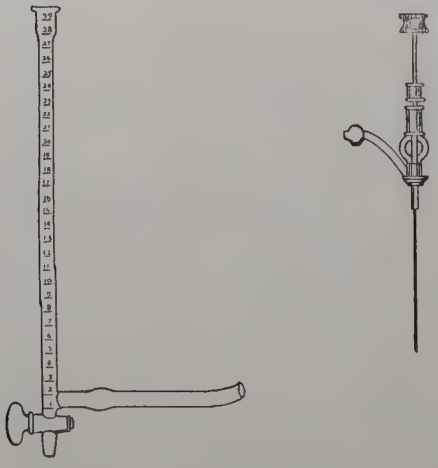

Fig. 16.—Apparatus of Fleischmann.

takes too much time to attach the glass tubing to the needle. It frequently happens that the pressure of the fluid is so great that as soon as the stylet is removed from the needle,

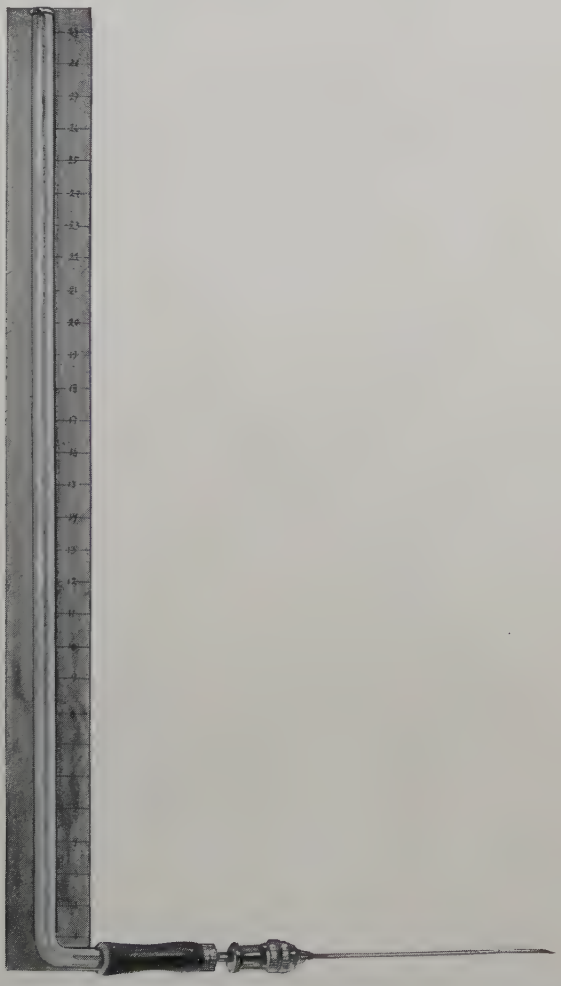

Fig. 17.—Modified Quincke apparatus for measuring the cerebrospinal fluid pressure.

the fluid gushes out, and several cubic centimeters of fluid are lost before the tip of the pressure apparatus can be connected to the needle.

(b) The second class of manometers consists of the U-tube mercury and water manometers (Figs. 18 and 19). Of these, the mercury manometer is to be preferred, for since less displacement occurs than when water is used, a closer approximate to the prewithdrawal pressure is obtained. Another advantage is that the mercury manometer is handier and more easily carried. The most widely used apparatus of this type is the Fleischer manometer (Fig. 19) which

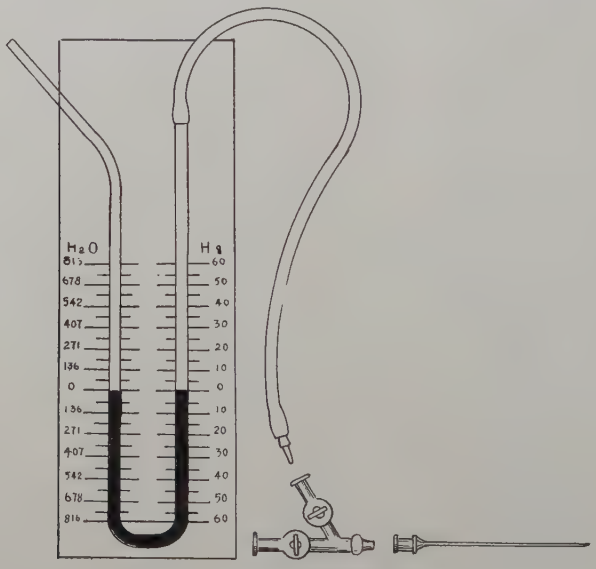

Fig. 18.—Apparatus of Neisser.

answers the ordinary clinical needs. A blood pressure manometer with the cuff detached has also been used. The objections to this type of manometer are that errors of observation are multiplied thirteenfold, respiratory and arterial oscillations in the manometer are too small to be gauged properly and here also exact prewithdrawal pressures are not obtained.

(c) Anaeroid or spring gauge types of manometers such as that of Claude (Fig. 20) or Ayala, are used extensively in Europe, especially in France. These have the advan-

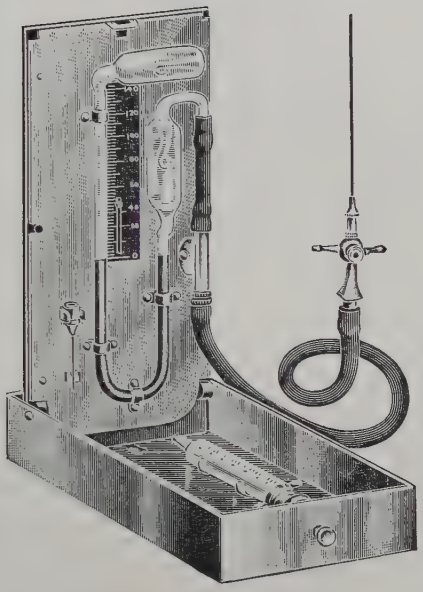

Fig. 19.—Fleischer's mercury manometer.

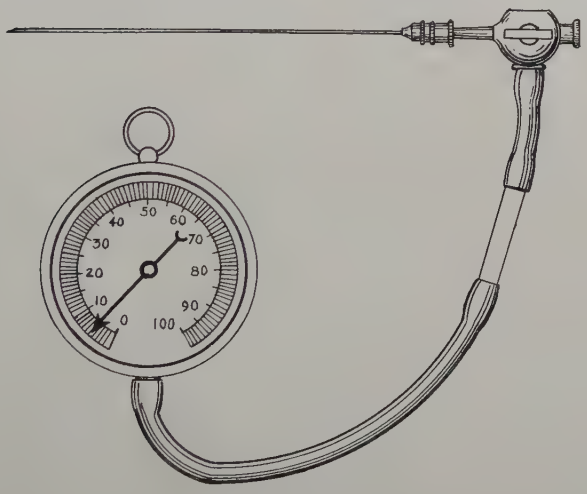

Fig. 20.—Apparatus of Claude.

tage of compactness. The disadvantage is that, in common with all spring instruments, they need frequent checking as the elasticity and resilience of the spring diminish.

(d) Prewithdrawal pressure manometers have been described by Kausch in 1908 and by Kilgore in 1927. The apparatus used by Kausch (Fig. 21) and later described again by Cassidy and Page, consists of a plain upright

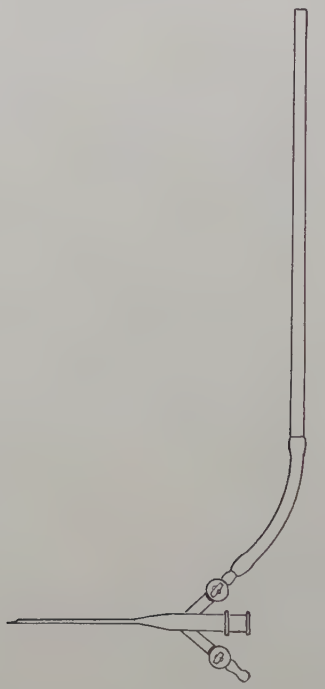

Fig. 21.—Apparatus of Kausch.

glass tube connected by a rubber tubing to a side opening in the needle. The glass and rubber tubing are filled to a certain mark with a sterile normal salt solution and the stopcock of the needle turned so that direct contact between the cerebrospinal fluid and the salt solution is obtained. The glass tubing is then raised or lowered until the salt solution returns to a level of the mark in the tube.

The difference in height between the level of the meniscus of the fluid and the puncture level indicates the prewithdrawal cerebrospinal fluid pressure in terms of height of salt solution. The serious disadvantage of this method is that it does not permit the securing of undiluted fluid for examination.

Kilgore has obviated this objection in an ingenious device, which uses a small rubber diaphragm between the

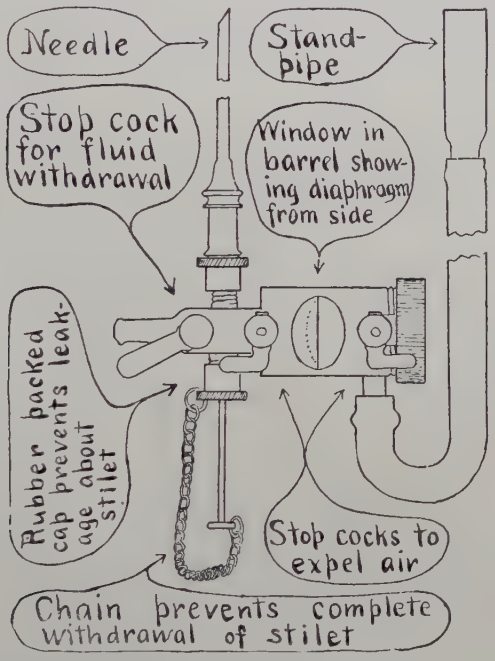
Needle
Stand-pipe
Stop cock for fluid withdrawal
Window in barrel showing diaphragm from side
Rubber packed cap prevents leakage about stilet
Stop cocks to expel air
Chain prevents complete withdrawal of stilet

Fig. 22.—Diagrammatic representation of Kilgore's cerebrospinal fluid manometer.

salt solution and the cerebrospinal fluid. Fig. 22 is a diagram taken from Kilgore's paper, and illustrates the mechanism of the needle. This apparatus has the objection of being expensive, of needing replacement of the rubber diaphragm at intervals and of being rather cumbersome. For clinical work, the greater degree of accuracy which Kilgore claims for it is not necessary.

In my experiments on pressure, I have originally used an apparatus which consisted of a needle to which was attached a small piece of glass tubing, to which in turn was attached a three-way stopcock. The manometer was made of glass tubing 800 mm. in length and one mm. in bore. However, because of the increased length of the needle, due to the glass window, and because of the possibility of breaking the glass I have discarded this arrangement. The outfit that I now use consists of a Luer detachable needle which can thus be easily replaced if broken, a stylet, and a three-way stopcock with a long hub. The advantage of this needle lies in the stopcock and its long hub, which prevents the loss of fluid. I have used this needle both with a straight glass tube manometer of one mm. bore and with the Fleischer manometer.

POSITION OF THE NEEDLE

The position of the needle in the canal is also responsible for a variation in pressure. An insertion which is too deep, or one that is too shallow will give readings lower than one that places the tip of the needle in the middle of the canal.

PREVIOUS WITHDRAWAL OF FLUID

As previously stated, the cerebrospinal fluid pressure falls rapidly as the fluid is withdrawn. The relation of the degree of reduction of fluid pressure to the amount of fluid drawn off is expressed by Ayala's "Quotient rachidien" in terms of $\frac{Q \times F}{I}$, where Q is the quantity of fluid withdrawn, F the final pressure and I the initial pressure. This quotient, in other words, is a measure of the rate of fall of pressure and is roughly proportional to the amount of cerebrospinal fluid present in the system. Quotients below 5 speak for brain tumor, and above 7 for serous

meningitis according to Balduzzi, although Greenfield and Carmichael have found low values in conditions other than brain tumor.

AGE

Quincke found pressure in children to be less than that in adults. He gives 40 to 60 mm. water (3 – 4.5 mm. of mercury) as the pressure in children, and 150 mm. water (11 mm. of mercury) as the pressure in adults. I also found the pressure to be lower in children than in adults. My figures showed a pressure variation of from 130 to 150 mm. water (9.5 – 11 mm. of mercury) in adults and 45 to 90 mm. water (3.5 – 7 mm. of mercury) in children in a quiet, recumbent posture. In the newly born I found the spinal pressure to vary between 1 to 6 mm. of mercury.

POSITION OF THE PATIENT

The position of the patient has a marked influence on the fluid pressure. In patients lying on one side with the spine horizontal and the head in alignment, the pressures in the ventricles, cisterns and lumbar spine are the same, according to Ayer. In the upright sitting position, he states that the lumbar pressure is approximately doubled, due to the hydrostatic pressure of the fluid, while the cistern and ventricular pressures fall below zero. The lumbar pressure was found by Krönig to be 120 mm. water (9 mm. of mercury) in the horizontal position, and 410 mm. water (30 mm. of mercury) in the sitting position; by Cottin and Saloz to be 200 – 230 mm. water (15 – 17 mm. of mercury) in the horizontal, and 400 – 420 mm. water (29.5 – 31 mm. of mercury) in the sitting position. I found the lumbar pressure in "normal" children under ten to be 150 – 230 mm. water (11 – 17 mm. of mercury) in the sitting position compared to 45 – 90 mm. water (3.5 – 7 mm. of mercury) in the recumbent position; in adults I found 130 – 150 mm. water

(9.5 – 11 mm. of mercury) in the recumbent, and 200 – 250 mm. water (15 – 18.5 mm. of mercury) in the sitting position. A cramped position increases the fluid pressure.

TABLE II

PRESSURE OF CEREBROSPINAL FLUID UNDER "NORMAL" CONDITIONS
(In mm. of Water)

AUTHOR	ADULT		CHILD (2 TO 10 YEARS)	
	LYING	SITTING	LYING	SITTING
Quincke	150		40-60	
Key and Retzius	160-200			
Falkenheim	160-200			
Falkenheim and Naunyn			50-200	
Adamkiewicz	80-100			
Krönig	125-150			
Boveri	170-200			
Sicard	200-300			
Cottin and Saloz	200-300			
Claude	150	240		
Bard	200	400		
Ayer	100-200			
Levinson	130-150	200-250	45-90	150-230

SITE OF PUNCTURE

There is a lack of agreement on the pressure reading in different loci. Wiegeldt states that in the horizontal position, ventricular pressure is normally a little higher than that in the subarachnoid space. Riser believes, to the contrary, that in the horizontal position, ventricular pressure is normally zero. Ayer states that normally the ventricular, cisternal and lumbar pressures are the same. Differences in pressures of fluid from different loci he believes are evidence of pathology; that is, subarachnoid block. He uses combined puncture to determine the site of the block; that is, double lumbar puncture for cauda equine lesions, cistern-lumbar puncture for cord, and ventricular-lumbar puncture for cerebellar fossa pathology. Normally, artificial elevation of the cerebrospinal fluid pressure, by pressure on the jugular vein, increases the reading in both manometers equally. In the presence of subarachnoid

block, the pressure reading in the manometer above the site of pathology is elevated alone or to a greater degree than that of the manometer below this site.

INTRACRANIAL ARTERIAL AND VENOUS PRESSURES

Intracranial arterial pressure has been shown to affect cerebrospinal fluid pressure. The very fact that the arterial pulsations are accompanied by fluctuations in the cerebrospinal fluid manometer indicates as much. In excitement, fear or any other condition which normally might raise the blood pressure, a corresponding rise in cerebrospinal fluid pressure occurs. In hypertension also, the fluid pressure is usually increased. Pike has found that in status epilepticus, cerebral hemorrhage, thrombosis and arteriosclerosis, as well as in the states of stupor and furore, the cerebrospinal fluid pressure is directly proportional to the arterial blood pressure. Conversely, following hemorrhages with lowering of the blood pressure, or in conditions such as shock or syncope (as may occur following spinal puncture) the fluid pressure is lowered. For this reason it has been suggested by Solomon, Thompson, and Pfeiffer that pressure readings should not be taken until ten minutes have elapsed after the puncture, to allow time for these physiologic effects upon the cerebrospinal fluid to pass over.

The cerebrospinal fluid pressure is even more intimately associated with venous than with arterial intracranial pressure. Magendie commented on the effect of the respiratory movements upon the pressure of the fluid. He observed that the cerebrospinal fluid showed movements corresponding to the respiration, the pressure falling during inspiration and rising during expiration. This observation has been confirmed by many workers. I have observed it frequently. The variation between inspiration and expiration, however, is small, the difference averaging from 10

to 15 mm. of water. This respiratory variation is dependent upon changes in intracranial venous pressure with which it is associated. In violent respiratory efforts, such as sneezing, coughing, hiccup or marked dyspnea, the increased cerebrospinal fluid pressure may cause the fluid to spurt to a distance of four to eight feet. A cramped position of the patient, by hyperflexion of the head or thighs, or arms held tightly to the sides, causing respiratory embarrassment, or jugular compression, results in a rise in cerebrospinal pressure.

The Queckenstedt Sign

In 1908, Neu and Hermann observed that constricting the neck caused a rise in cerebrospinal fluid pressure. Queckenstedt showed that the compression of the external jugular vein with subsequent rise of venous pressure in the cranial cavity was responsible for this rise. The Queckenstedt sign of rise in fluid pressure on compression of the external jugular vein is present in normal individuals. Its absence usually signifies subarachnoid block or lateral sinus thrombosis.

RATE OF FORMATION AND RATE OF ABSORPTION

Attention has been called by several observers to the influence of the rate of formation of cerebrospinal fluid upon the fluid pressure. The rate of formation or what is commonly spoken of as "secretion pressure" in a given individual is normally subject to physiologic variation, being increased in hyperemic and inflammatory conditions of the cranium and decreased by those conditions that cause a lessening of the blood supply of the chorioid plexus. It frequently happens that a spinal puncture done several hours after fluid has been withdrawn, reveals a pressure as high or even higher than the pressure previously recorded. This is due to the replacement of fluid by an increased "secretory" rate. In inflammations of the brain and meninges, there is an increased "secretory" pressure.

The same theoretical conclusions apply to rate of absorption as to rate of formation. An increased rate of absorption will cause a lowering of the fluid pressure and vice versa. Under normal conditions, such changes probably occur in response to physiologic stimuli. Under pathologic conditions, such as obstructive hydrocephalus, it is definitely the failure of the fluid to be absorbed that causes the marked increase in ventricular pressure.

BRAIN VOLUME

Since the skull and spinal column form a rigid container for the central nervous system, any changes in volume within this system must be compensated for by changes in pressure. Weed and McKibben and later Foley and Putnam showed that it is possible to reduce the cerebrospinal fluid pressure and diminish the bulk of the brain by injecting a hypertonic solution into the blood stream. Hypotonic solutions have the opposite effect. Cushing and Foley showed that the same effects could be produced by the gastrointestinal route of administration. They applied this procedure clinically to patients suffering from "pressure symptoms" due to increased intracranial pressure and were able to cure or alleviate these symptoms by administering hypertonic salt solution. Kinsman, Spurling, and Jelsma have shown that the mechanism of this reaction is dependent upon the loss of water from the brain substance. Kubie and Hetler have shown that following the intravenous injection of hypertonic solutions, there is a narrowing of the vessels of the pia coincident with a dilatation of the vessels of the cortex itself; and following the intravenous injection of distilled water there is a dilatation of the vessels of the pia, but a blanching of the cortex itself.

Summary

In the present state of our knowledge, the data on the actual prewithdrawal pressure of cerebrospinal fluid are very meager. Most figures on pressure given in the litera-

ture have been obtained with manometers that measure the pressure after the cerebrospinal fluid has filled the measuring apparatus.

Under normal conditions, the cerebrospinal fluid pressure is from 100 to 200 mm. of water, with an average of 135 mm., for an adult lying down. For a child it is approximately one-half this amount. In the sitting position, the lumbar pressure is approximately double that in the recumbent posture.

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CHAPTER V

NORMAL CEREBROSPINAL FLUID
PHYSICAL AND PHYSICOCHEMICAL PROPERTIES

The term "normal" as applied in the literature to cerebrospinal fluid is often misleading. The mere fact that cerebrospinal fluid has been removed from a living person is indicative of the presence of some abnormality of the nervous system that prompted the puncture. Often the bacteriologic and qualitative chemical tests on a given specimen of fluid are negative, yet quantitative chemical analysis will show an alteration in the chemistry or physical chemistry of the fluid. Many of the earlier data on normal cerebrospinal fluid have been based upon studies made on fluid obtained postmortem. Such fluid, however, can hardly be considered normal, for it has usually undergone marked chemical and physicochemical changes before examination. For instance, fluid removed postmortem has been shown by Myers to contain three and one-half times as much potassium oxide as fluid removed during life. Cotton and Ayer found a preponderance of endothelial cells in postmortem fluid. I also found a marked difference between fluid removed during life and after death. In the former case the fluid was slightly alkaline and in the latter, distinctly acid. "Normal" as applied to cerebrospinal fluid should, therefore, be considered merely as a relative term, indicating that the fluid was obtained from a person not suffering from organic disease of the central nervous system.

In the discussion following in this chapter I shall state so far as possible the diagnosis of the case, whether the cerebrospinal fluid in question was withdrawn during life or postmortem, and whether it was obtained by spinal, ventricular or cistern puncture.

PHYSICAL PROPERTIES

Amount

The amount of fluid normally present in the ventricles and in the subarachnoid space has been variously stated. Cotugno found between 125 and 156 c.c. in both; Magendie found between 62 and 372 c.c. According to Magendie, the normal amount of cerebrospinal fluid in a medium-sized man is 62 c.c. Of this amount, Magendie says, the ventricles contain from 20 to 30 c.c., and the subarachnoid space of the cord the greatest part of the remainder. Luschka found only 25 c.c. Testut estimated the amount to be between 100 and 150 c.c. Fontecilla and Sepulveda measured the quantity of cerebrospinal fluid in three healthy subjects who had died in an accident, and found that the amount was 128-130 c.c. It may be interesting to note that although there is from 60 to 150 c.c. of cerebrospinal fluid present in the subarachnoid space and the ventricles, it is generally inadvisable and often impossible to remove more than 10 c.c. of fluid from a patient at one sitting.

Color

Normal cerebrospinal fluid is clear and colorless, provided no blood has been removed with it during the puncture. The fluid does not change color upon standing if it is corked or plugged with a cotton plug, unless, of course, it has become contaminated by bacteria or moulds, in which case the fluid becomes turbid.

Lack of Sediment

Normal cerebrospinal fluid forms no pellicle or sediment of any kind. This is because of the fact that the cell content, as well as the protein content, is very small, and fibrin is either entirely absent or present only in very small

traces. The lack of sediment is helpful in differentiating normal or nonmeningitic fluid from fluid in cases of meningitis in which a sediment is often present.

PHYSICOCHEMICAL PROPERTIES

There is no line of scientific investigation where so many factors enter into the results obtained as in physicochemical determinations. Temperature, barometric pressure and especially the length of time the fluid has been standing before it is examined count a great deal. So it is that while the chemical data found in the literature of several years ago are in the main confirmed by newer investigations, some of the older physicochemical data are found incorrect when newer methods are used, and when the various factors influencing physicochemical findings are taken into consideration. Especially is this true with regard to the reaction of the cerebrospinal fluid and the alkali reserve.

Specific Gravity

As can be noted from Table III, the specific gravity of cerebrospinal fluid has been found by various writers to range from 1.001 to 1.010.

Table III

AUTHOR	SPECIFIC GRAVITY
Hoppe	1.001 -1.005 (hydrocephalus)
Halliburton	1.007 -1.008
Kafka	1.002 -1.008
Zdarek	1.007
Polányi	1.005 -1.007
Mestrezat	1.00759 (20° C.)
Nawratzki	1.0073 -1.008 (same for horse)
Pende	1.007 -1.010
Borelli and Data	1.007 -1.009
Williamson	1.005 -1.009
Hammersten	1.007 -1.008
Eskuchen	1.006 -1.007
Levinson	1.0034 -1.0070

In my series of cases, I used the pyknometer for the determination of the specific gravity of cerebrospinal fluid.

Conductivity

Polányi found the conductivity of cerebrospinal fluid in a case of hydrocephalus to be 0.01136; 0.01280; 0.01527; and 0.01452 at 20° C. Eckel found the conductivity to vary between 0.01549 and 0.01425, with an average of 0.014967. The conductivity, he showed, depends upon the total ionized solids present in the fluid, these being mainly in the form of sodium chloride. This explains the decreased conductivity of the cerebrospinal fluid in tuberculous meningitis. The age of the fluid according to Eckel, does not affect its conductivity. A slight decrease in conductivity occurs if there is a great increase in the protein content of the fluid. In my experiments, the conductivity of nonmeningitic fluid was 0.01513; 0.01365; and 0.01513 at 25° C.

Surface Tension

Polányi found the surface tension to be 7.35, 7.15, 7.16 and 7.20 dynes at 20° C. Ascoli-Izar found it to vary between 101 to 105 stalagmometer drops, which is slightly less than water.

Viscosity

Table IV gives the figures of different workers.

Table IV

AUTHOR	VISCOSIMETRIC INDEX
Borelli and Data	1.059 -1.049
Galletta	1.008 -1.024
Valeusi	1.000 -1.105
Polányi	1.020 -1.027 at 38° C.
Eskuchen	1.01 -1.06
Levinson	1.0424-1.0489 using Ostwald apparatus
Levinson and Serby	1.04 -1.09 using Hess apparatus

Refractometric Index

Polányi found the refractometric index of the cerebrospinal fluid to be 1.3499 at 23° C; 1.33516 at 21° C; 1.33579

at 20.3° C; and 1.33554 at 20° C. Serby and I found it to vary between 1.33472 and 1.33545, with an average of 1.33508. The viscosimetric and refractometric indexes are unaffected by the age of the cerebrospinal fluid. They are useful in determining a marked increase in the protein content of the cerebrospinal fluid but not a slight increase in protein.

Freezing Point

The freezing point of cerebrospinal fluid varies between –0.51 and –0.75° C., depending upon the investigator (Table V).

TABLE V

AUTHOR	FREEZING POINT (DEGREES BELOW 0° C.)
Levi	0.59
Sollmann	0.535
Fuchs and Rosenthal	0.53
Pende	0.59
Grenet	0.38 to 0.56
Quincke	0.56 to 0.75
Mott	0.51 to 0.56
Polányi	0.566 to 0.678
Mestrezat	0.57 to 0.59
Depisch and Richter-Quittner	0.56 to 0.60
Eskuchen	0.52 to 0.58
Levinson	0.56 to 0.58

Spectroscopic Analysis

Shionoya observed that normal cerebrospinal fluid has a "normal absorption curve," which can be plotted from the absorption bands found in the spectrum of the cerebrospinal fluid. He found that a deviation from this curve was proportional to the amount of protein present in the fluid.

Crystallization

I evaporated a number of specimens of cerebrospinal fluid, after precipitating and filtering off the protein. The resultant crystals (Figs. 23 and 24) resembled those of sodium chloride (Fig. 25) in most respects. The crystals dissolved in water very easily.

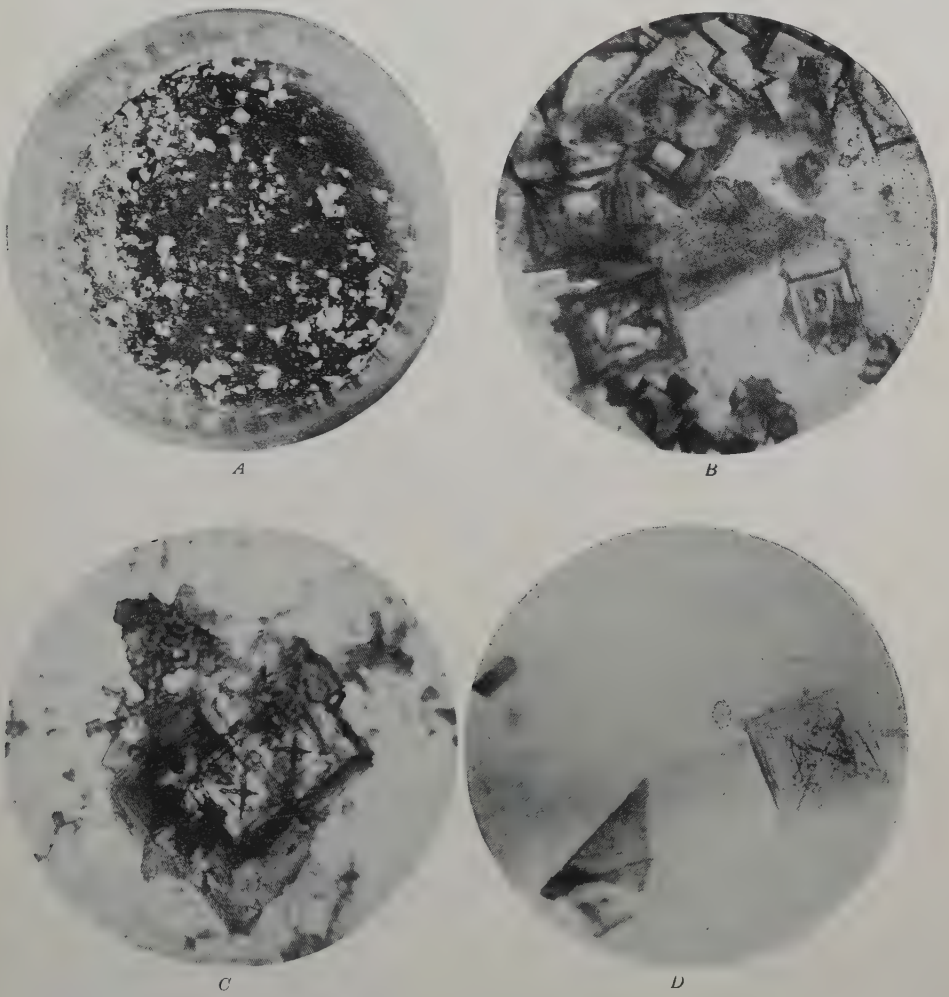

Fig. 23.—Crystallization of nonmeningitic cerebrospinal fluid.

A. Crystals obtained after the protein has been removed from the fluid by precipitation and the filtrate evaporated on steam bath. (Natural size.)

B. Same fluid showing the crystals. (Magnified 24 times.)

C. Clump of crystals of same fluid. (Magnified 45 times.)

D. Single crystal. (Magnified 45 times.)

Fig. 24.—Crystals of evaporated nonmeningitic cerebrospinal fluid. (Magnified 24 diameters.)

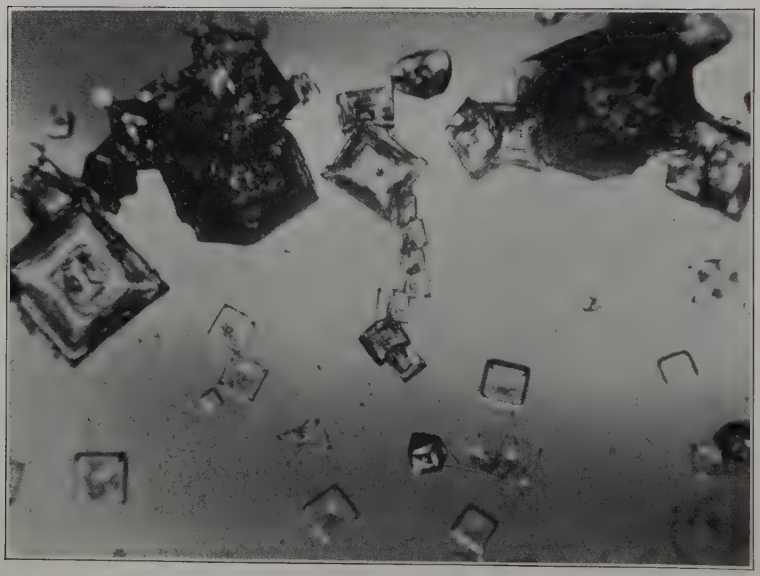

Fig. 25.—Crystals of sodium chloride in a 1 per cent solution of dextrose. (Magnified 24 diameters.)

Reaction of Normal Cerebrospinal Fluid

All through the older writings, the statement is found that the cerebrospinal fluid is alkaline in reaction, the alkalinity being given as a rule as half that of the blood. Cavazzani examined the fluid of two cases of hydrocephalus, and found it neutral in reaction. Concetti found the fluid alkaline three times, and weakly alkaline four times. Von Jaksch found the alkalinity to equal 20 c.c. of n/10 acid solution.

Kafka used n/10 HCl and cochineal as an indicator, and found that on an average, 20 c.c. of acid was necessary to neutralize 100 c.c. of fluid. According to Mott, the alkalinity of the fluid corresponds to 0.1 per cent of sodium hydroxide.

Of late, the entire conception of the reaction of body fluids has changed due mainly to the work of Michaelis, Sörenson, Henderson and Van Slyke. The reaction of body fluids is now spoken of in terms of hydrogen and hydroxyl ions, which is expressed either in the terms of hydrogen-ion concentration, or in terms of P_H, the latter term indicating the negative exponent of the hydrogen-ion concentration, for instance $P_H\ 7.1 = 1 \times 10^{-7.1}N$. The H-ion concentration can be determined in a number of ways, the most important of which are the compensation method of Michaelis or of Hildebrandt, and the indicator method of Sörenson. Practically all of these methods have been used recently for the study of the cerebrospinal fluid. The results, however, have not been uniform. Bisgaard examined the fluid against a borate mixture, 5.7 plus HCl, and found that the fluid was more acid than the borate mixture. Polányi determined the H-ion concentration of one fluid drawn from a case of hydrocephalus, by the compensation method with the use of the Farkas-Szilisch electrode. He found the H-ion concentration to be 9.084 $\times 10$. Hurwitz and Tranter, who used the Levy Rowntree-Marriott standards, found the P_H of normal fluids

to vary between 8.15 and 8.30 with an average of 8.26, this being somewhat lower when the fluid was dialyzed, the average then being 8.11. Weston found the dialyzed fluid to vary between 7.9 and 8.3 with an average of 8.12. Felton, Hussey and Bayne-Jones, using the Levy-Rowntree-Marriott method, found the reaction of cerebrospinal fluid to vary between P_H 7.7 and 7.9 when examined immediately after removal from the body and P_H 8.7 when examined after the fluid has stood for some time.

TABLE VI

H-ION CONCENTRATION OF NORMAL CEREBROSPINAL FLUID BY OTHER AUTHORS

AUTHOR	METHOD EMPLOYED	P_H FRESH	P_H OLD	REMARKS
Cavazzani	Tartaric acid	Neutral Interval of standing not indicated.		2 cases of hydrocephalus.
Concetti		Alkaline 3 times, weakly acid 1 time. Interval of standing not indicated.		
Myers	Litmus	Neutral or faintly alkaline		
Bisgaard	Phenolphthalein	Less than 8.1		
Kopetzky	Litmus	Less than 8.0		
Turner	Phenolphthalein	Acid		Fluid in stoppered bottles retained acidity Fluid in unstoppered bottles became alkaline
Polányi	Farkas-Szilisch electrode		9.0	
Hurwitz and Tranter	Levy-Rowntree-Marriott method		8.15 8.30 average-8.1	
Weston	Levy-Rowntree-Marriott method		7.9-8.3 average-8.12	
Felton, Hussey and Bayne-Jones	Levy-Rowntree-Marriott method	7.7-7.9	8.6	

I have examined the H-ion concentration in over four hundred normal cerebrospinal fluids, or to be more accurate, fluid from cases that proved to be nonmeningitic in character. The series included cases of nephritis, gastrointestinal intoxication, pneumonia, paresis, alcoholic psychosis, dementia precox, brain tumor, epilepsy and many other conditions. I used the methods of Michaelis and Hildebrandt for the determination in old fluids and the Levy-Rowntree-Marriott method, or an indicator corresponding to this method, in fresh fluid. I found that when the fluid is examined immediately after its withdrawal from the body, the H-ion concentration, expressed in terms of P_H ranges from 7.4 to 7.6. In only two cases have I found an H-ion concentration of fresh fluid to be 7.7. However, if the fluid has been standing a short while, the reaction changes very quickly toward the alkaline side. As a rule, standing half an hour changes the reaction to a P_H of 7.5 to 7.6; standing one hour changes the reaction to a P_H of 7.7; standing two hours changes it to 7.9 or 8.0. From two hours on, the change in the reaction toward the alkaline side is rather small, some fluids changing in twelve hours to 8.1, and remaining at this concentration no matter how long it stands; other fluids changing to 8.3 or even 8.6 in course of twenty-four hours or longer.

In Table VII, I give the H-ion concentration in some of my cases showing average results, indicating the method used by the letters a, b, c; "a" represents the gas-chain method, "b" the alkalinized phenolphthalein compared to the Sörenson standards, and "c" the Levy-Rowntree-Marriott indicator compared to the standard colorimetric tubes. A typical change in the H-ion concentration is illustrated in the curve shown in Fig. 26. The results obtained by phenolphthalein compared to the Sörenson standards, are often marked with an additional + and – signs. This means that P_H of the cerebrospinal fluid was higher or lower than the figure given, but how high or how low was not determined.

These findings have been so constant that I believe we can account for the high P_H obtained in normal cerebrospinal fluid by the authors quoted. They examined the fluid after it had been standing for some time, which naturally gave a very low H-ion concentration, or a high P_H. Interesting in this connection is the work of John Turner who not only knew of the high H-ion concentration of the fluid, but was also aware of the fact that the concentration changes on standing. To quote him:

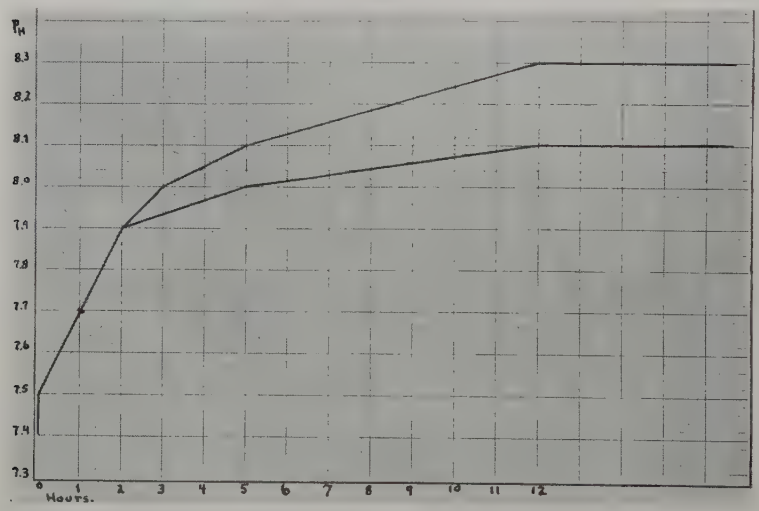

Fig. 26.—Changes in the H-ion concentration of two nonmeningitic fluids on standing.

"In all the cases of this series and in twenty examined fifteen years ago, I have obtained an alkaline reaction (and not amphoteric) to litmus paper, but with phenolphthalein the great majority have an acid reaction. The degree of acidity, however, is in many cases very slight. A very faint pink solution of phenolphthalein was poured into two small beakers, so that the tint in both was similar in looking down at them as they stood upon a porcelain slab. A little of the fluid was then added to one beaker and generally the pink color was immediately discharged. I

found that the fluid left unstoppered in my room, where gas is constantly burning, rapidly becomes alkaline, whereas similar fluid in stoppered bottles retained its acidity, and that in my later examinations where this source of fallacy was recognized and excluded, the results tend more and more to be uniformly acid with phenolphthalein."

I have endeavored to find the factors that are responsible for the changes taking place in the H-ion concentration of nonmeningitic cerebrospinal fluid. I found that when I put a part of the cerebrospinal fluid right after its withdrawal from the body into a desiccator containing twenty per cent sodium hydrate, and allowed it to remain in the desiccator from ten to thirty minutes, the acidity of the fluid was greatly decreased, the P_H being in a very short time 7.7 to 7.9.

This shows that the removal of CO_2 from the fluid causes a decrease in the H-ion concentration of the fluid. To make certain, however, that the increase in the P_H of the cerebrospinal fluid is entirely due to CO_2, I performed the following experiment. I divided a fluid into two portions: one portion I corked tightly after its removal from the body, and coated with a layer of paraffin, and the other portion I left in a nonsol glass tube. The two portions of the fluid were examined twenty-four hours later. I found that the fluid which had been corked very tightly retained the original H-ion concentration, giving a P_H of 7.4 to 7.6 in twenty-four hours; while the fluid that had been left in a cotton plugged test tube gave a P_H of 8.1 or higher in twenty-four hours, which is the ordinary change taking place in cerebrospinal fluid. This shows that the decrease in the H-ion concentration in the cotton-plugged tube was not due to formation of ammonia or other alkaline substance, but to the loss of CO_2 from the fluid into the air. I have furthermore shown that when the tube containing fluid is corked tightly, but some space is left between the fluid and the cork, there will be some change in the H-ion

TABLE VII

H-ION CONCENTRATION OF NONMENINGITIC SPINAL FLUID

CASE	DIAGNOSIS	P_H			
		Immediate	½ Hour	1 Hour	2 Hours
1	Little's disease				
2	Tetanus				
3	Pneumonia				
4	Gastro-enteritis				
5	Brain tumor				
6	Endarteritis				
7	Typhus				
8	Brain tumor				
9	Tic				8.0 (b)
10	General paresis				8.0 (b)
11	Delirium tremens				
12	General paresis				
13	Psychosis				
14	Tubercle of brain	7.4 (b)			
15	Juvenile paresis	7.4 (b)			
16	Alcoholic		7.4 + (b)		
17	General paresis		7.4 + (b)		
18	Alcoholic				
19	Paranoia	7.5 (c)			
20	Epilepsy	7.4 (c)			
21	Epilepsy		7.5 (c)		
22	C. Sp. Lues ?			7.9 (c)	
23	Paresis			7.7 (c)	
24	Psychosis			7.7 (c)	
25	Psychosis	7.5 (c)			
26	Psychosis	7.6 (c)			
27	Psychosis	7.5 (c)			
28	Psychosis	7.5 (c)			
29	Brain tumor				8.0 (c)
					8.0 (b)
30	Pneumonia				
31	Alcoholic	7.4 (c)	7.4 (c)	7.5 (c)	7.9 (c)
32	General paresis	7.4 (c)			
33	Psychosis	7.7 (c)			
34	Psychosis	7.5 (c)			
35	Alcoholic	7.4 (c)			
36	Psychosis	7.4 (c)			
37	Psychosis	7.5 (c)			
38	Alcoholic	7.5 (c)			
39	Alcoholic	7.4 (c)			
40	General paresis	7.5 (c)			
41	Psychosis	7.4 (c)	7.6 (c)		
Mixture		7.4 (c)	7.8 (c)		
42	Psychosis	7.4 (c)			
43	Psychosis	7.5 (c)			
Mixture	Psychosis	7.4 (c)			
Mixture					
44	Poliomyelitis			7.7 (c)	
Mixture	General paresis	7.4 (c)			
45					
46	Pneumonia	7.7 (c)			
Mixture		7.4 (c)			
47		7.4 (c)			
48	Psychosis	7.5 (c)			
49	Meningism	7.5 (c)			
50	Poliomyelitis ?		7.6 (c)		

(Continued on p. 101.)

concentration of the fluid, the H-ion decreasing slightly although not nearly as much as the fluid standing in the cotton-plugged tube (Table IX) (Fig. 27). I have also

TABLE VII—CONTINUED

H-ION CONCENTRATION OF NONMENINGITIC SPINAL FLUID

P_H						
3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days and Over
						8.56 (a)
						8.14 (a)
						8.6 (a)
						9.08 (a)
						8.3 (a)
						7.89 (a)
					8.0+(b)	
					8.6—(b)	
						8.6—(b)
					8.0+(b)	
						8.6—(b)
			8.0 (b)			
		8.6—(b)				
	8.0 (c)					
		8.0 (c)				8.4 (c)
						8.2 (c)
		8.0 (c)	8.1 (c)	8.1 (c)		
			8.1 (a)			
	8.1 (c)					
		8.1 (c)	8.1 (c)			
				8.1 (a)		
				8.1 (c)		
				8.1 (a)		
				8.1 (c)		
				7.7 (a)*		
				7.7 (c)		
				8.1 (c)		
		8.1 (c)				
		8.1 (c)				8.1 (c)
					8.2 (a)	
			8.1 (a)			
					8.2 (c)	

* Corked.

measured the total carbonates in fresh and old fluid and found it to run parallel with the H-ion concentration as shown in Table VIII. To show further that ammonia, even

TABLE VIII

CHANGES IN H+ CONCENTRATION ON REMOVAL OF CO_2 BY EXPOSURE TO ALKALI IN DESICCATOR

CASE	FLUID DRAWN	PH IMMEDIATELY	EXPOSED TO ALKALI	EXPOSED TO AIR	EXAMINED	PH.
190	6:55 p. m.	7.4	12 minutes		7:07 p. m.	7.7-7.8
190	6:55 p. m.	7.4	20 minutes		7:15 p. m.	7.8
190	6:55 p. m.	7.4	20 minutes	7 minutes after 20 minutes exposure to alkali	7:22 p. m.	7.8-7.9
190	6:55 p. m.	7.4	27 minutes	38 minutes after 27 minutes exposure to alkali	7:55 p. m.	7.8-9
190	6:55 p. m.	7.4	20 minutes	13 hours	11:22 a. m.	8.1
188	7:03 p. m.	7.4	10 minutes		7:13 p. m.	7.7-7.8
188	7:03 p. m.	7.4	30 minutes		7:33 p. m.	7.8
188	7:03 p. m.	7.4	30 minutes	3 minutes	7:36 p. m.	7.8
186	7:45 p. m.	7.4	6 minutes		7:51 p.m.	7.6-7.7
186	7:45 p. m.	7.4	25 minutes		8:10 p. m.	7.9

if absorbed from the air, is a negligible factor, I made the following experiment: A fluid was divided into two portions, one of which was exposed to ammonia-free air in a

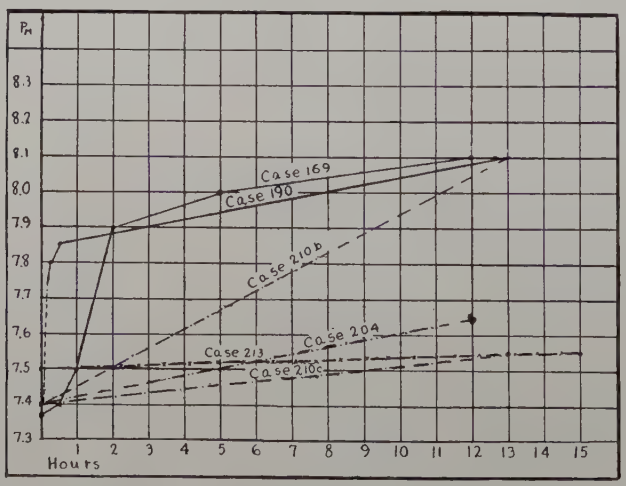

Fig. 27.—Change in H+ concentration of nonmeningitic fluids on standing at room temperature under various conditions. Case 169. Plugged with cotton. Case 190. Immediately after withdrawal, exposed to CO_2 free air in desiccator (dotted line) and later left with cotton plug. Case 210b. Plugged with cotton; Case 210c, the same fluid as b, but corked with a cork—a few bubbles at the top. Case 204. Six c.c. tube, half filled, and tightly corked; cotton-plugged fluid was same as Case 210b (8.1). Case 213. Almost perfectly sealed with cork, without any air bubble above the fluid.

TABLE IX

H + CONCENTRATION OF FLUIDS STANDING IN CORKED TUBES

NUMBER	AGE	DIAGNOSIS	INTERVAL	STOPPERED WITH	P_H
Mixture					
210a	27	Alcoholic	Immediately		7.4
	38	Alcoholic	Immediately		7.4
210b	27	Alcoholic			
	38	Alcoholic	13 hours	Cotton	8.1
210c	27	Alcoholic	12 hours	Paraffined cork (few bubbles below cork)	7.5–7.6
	38	Alcoholic			
211a	43	Alcoholic	Immediately		7.5
	46	Alcoholic	Immediately		
211b	43	Alcoholic		Cotton	
	46	Alcoholic	12½ hours		8.1
211c	43	Alcoholic	12½ hours	Paraffined cork	7.5–7.6
	46	Alcoholic			
211d	43	Alcoholic	15½ hours	Paraffined cork replaced after 3 c.c. removed for exam. at 8:10, leaving 3 c.c. space in 6 c.c. tube.	
	46	Alcoholic			7.6
212	55	Alcoholic	4 minutes		7.4
b	55	Alcoholic	15 hours	Paraffined cork	7.5–7.6
c	55	Alcoholic	15 hours	Cotton	8.2
d	55	Alcoholic		Cotton	7.9
213	39	Alcoholic	2 minutes		7.5
b	39	Alcoholic	15½ hours	Paraffined cork	7.5–7.6
218	1 yr.	Pneumonia	Immediately		7.5–7.6
b	1 yr.	Pneumonia	47 hours	Paraffined cork	7.5–7.6
c	1 yr.	Pneumonia	47 hours	Cotton	8.2
204	46	Pulmonary tuberculosis	15 minutes		
	42	Alcoholic	10 minutes		7.4
	38	General paresis	Immediately		
b	38	General paresis	12 hours	Cotton	8.1
c	38	General paresis	12 hours	Paraffin; left 3 c.c. space above volume of liquid.	7.6–7.7
205	29	Alcoholic	11 minutes		
	34	Alcoholic	8 minutes		7.4
	36	Alcoholic	Immediately		
b	36	Alcoholic	12 hours	Cotton	8.1
c	36	Alcoholic	12 hours	Paraffined; 1 c.c. of space eft on top of fluid	7.5–7.6

Table X

Physical Constants of Cerebrospinal Fluid

Author	Total amount present (in c.c.)	Pressure (in mm. of water; for adults lying down)	Specific gravity	Conductivity	Surface tension (in dynes)	Freezing point (°C.)	Viscosity ($H_2O = 1$)	Refractometric index ($H_2O = 1$)	Ph	CO_2 combining power
Cotugno	125 to 156									
Magendie	62 to 372									
Mott	100 to 150					−0.51 to −0.56				40%
Fontecilla and Sepulveda	128 to 130	(sitting 60 to 150)								
Testut	100 to 150									
Quincke		150 (child 40 to 60)				0.56 to −0.75				
Key and Retzius		160 to 200								
Falkenheim		160 to 200								
Falkenheim and Naunyn		(child 50 to 200)								
Cybierski		72 to 90								
Adamkiewicz		80 to 100								
Kroenig		125 to 150								
Boveri		170 to 200								
Sicard		200 to 300								
Cottin and Saloz		200 to 300								
Claude		150 (sitting 240)								
Bard		200 (sitting 400)								
Ayer		100 to 200								
Halliburton			1.007 to 1.008							
Kafka			1.002 to 1.008							
Polányi			1.005 to 1.007	0.01136 to 0.01527 (20° C.)	7.15 to 7.35 (20° C.)	−0.566 to −0.67	1.020 to 1.027 (38° C.)	1.33516 to 1.33579 (20 to 23° C.)	9.0	

TABLE X—CONT'D

PHYSICAL CONSTANTS OF CEREBROSPINAL FLUID

AUTHOR	TOTAL AMOUNT PRESENT (IN C.C.)	PRESSURE (IN MM. OF WATER; FOR ADULTS LYING DOWN)	SPECIFIC GRAVITY	CONDUCTIVITY	SURFACE TENSION (IN DYNES)	FREEZING POINT (°C.)	VISCOSITY (H_2O = 1)	REFRACTOMETRIC INDEX (H_2O = 1)	pH	CO_2 COMBINING POWER
Zdarek			1.007							55%
Mestrezat			1.00759			–0.57 to –0.59				
Nawratzki			1.0073 to 1.008							
Hoppe			1.001 to 1.005							
Pende			1.007 to 1.010			–0.59				
Borelli and Datta			1.007 to 1.009				1.049 to 1.059			
Eskuchen			1.006 to 1.007			–0.52 to –0.58				
Eckel				0.01425 to 0.01549						
Ascoli-Izar					101 to 105 Stalagmometer drops					
Levi						–0.59				
Sollman						–0.535				
Fuchs and Rosenthal						–0.53				
Grenet						–0.38 to –0.56				
Depisch and Richter-Quittner						–0.56 to –0.60				
Galletta							1.008 to 1.029			
Valeusi							1.000 to 1.105			
Felton, Hussey and Bayne-Jones									7.7 to 7.9	
McClendon									7.45	60%
Hurwitz and Tranter									8.1	
Weston									8.12	
Levinson		130 to 150 (child 45 to 90)	1.0034 to 1.007	0.01365 to 0.01513 (25° C.)		–0.52 to –0.58	1.04 to 1.09	1.33472 to 1.33545	7.4 to 7.6	45.7% to 63%

desiccator, and the other left at the ordinary laboratory temperature. After thirty minutes I examined the two fluids for their H-ion concentration and found it to be the same in both cases, showing that the usual decrease in the H-ion concentration of a fluid is not due to absorption of ammonia from the air.

When we compare H-ion concentration of normal cerebrospinal fluid with that of the blood, we find that they are both the same. The H-ion concentration of the blood also ranges between a P_H of 7.4-7.6 immediately after being removed from the body.

Alkali Reserve

I determined the alkali reserve or the amount of CO_2 present in the cerebrospinal fluid as bicarbonate, by means of the Van Slyke alkali reserve apparatus. Table XI shows the alkali reserve in nonmeningitic fluid:

TABLE XI

ALKALI RESERVE OF NONMENINGITIC CEREBROSPINAL FLUID

NO.	DIAGNOSIS	ALKALI RESERVE
1.	Tabes	56.5
2.	Poliomyelitis	45.7
3.	Uremic coma	52.0
4.	Meningism	47.5
5.	Chorea	63.0
6.	Dementia precox	58.75
7.	Psychosis	55.72
8.	Cerebrospinal lues	55.72
9.	Psychosis	57.54

The above shows that the alkali reserve of nonmeningitic cerebrospinal fluid varies between 45.7 and 63.0%, the greatest number being between 52 and 57% of CO_2 bound by the cerebrospinal fluid at 0° C. temperature, at 760 mm. Hg. barometric pressure, which is about the same as the alkali reserve of blood.

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CHAPTER VI

NORMAL CEREBROSPINAL FLUID CHEMICAL PROPERTIES

In spite of the large amount of work done on the chemical composition of the cerebrospinal fluid, there are many fundamental questions pertaining to the chemistry of this fluid that have not yet been answered. The reason that our information regarding the chemistry of cerebrospinal fluid is not so definite and so accurate as it might be, is that the amount of fluid one is obliged to work with under normal conditions is usually so small (5 to 10 c.c.) that it hardly permits a complete quantitative analysis.

It is but recently that microchemical methods have been devised for body fluids, and even now, with improved methods, it is hardly possible to make an entire quantitative analysis on one specimen of normal cerebrospinal fluid. This scarcity of fluid necessitates working on one chemical substance at the time or the use of a mixture of fluids for the determination of the various chemical constituents, a procedure adopted by Mestrezat. One can readily see that data gathered in this way cannot be very accurate, especially since the chemical character of the fluid is affected by such factors as the condition of the patient, and the age of the fluid. It is surprising to note, however, that with all of the drawbacks some of the chemical determinations of the very early investigators still hold good, particularly the determinations of the organic matter, and of the amount of the total solids and chlorides.

I shall present here data obtained from the literature, following the experiments as far as possible in chronologic order to show the evolution of chemical methods as applied to cerebrospinal fluid.

Early Investigations

One of the earliest determinations of the chemical composition of cerebrospinal fluid was that of Lassaigne who examined the cerebrospinal fluid of a horse after death. The fluid was obtained for the chemist by Magendie. The analysis gave the following composition per 100 parts:

Water	98.180
Osmazome	1.104
Protein	0.033
Sodium chloride	0.610
Sodium bicarbonate	0.060
Phosphate and traces of calcium carbonate	0.009

Lassaigne could not find any soluble phosphates in the liquor.

The same author examined the cerebrospinal fluid of an old woman and found the following per 100 parts:

Water	98.564
Osmazome	0.474
Protein	0.088
Sodium and potassium chloride	0.801
Animal matter and free calcium phosphate	0.036
Sodium carbonate and calcium phosphate	0.017

Among the early workers in this field was Hoppe. He made a chemical analysis in two cases of spina bifida and three cases of internal hydrocephalus. In one case of spina bifida, he removed 22 to 35 c.c. of cerebrospinal fluid at a sitting. (The author unfortunately does not give the method he employed in the removal of the fluid.) He found the fluid very alkaline. (Here again the author does not say what indicator he used, or how long after removal of the fluid from the body, he examined it). On heating, the fluid became slightly turbid, but on addition of acetic acid, flocculi appeared. The fluid reduced copper oxide and gave the following quantitative results in grams per 1000:

	FIRST PUNCTURE	SECOND PUNCTURE	THIRD PUNCTURE
Protein	1.62	2.64	2.46
Water extractive	0.70	0.35	0.42
Alcohol extractive and soluble salt	9.57	2.48 7.52	2.23 8.21
Insoluble salt	0.25	0.15	0.28
Giving—			
Dry substance	12.51	13.12	13.28
Water	987.49	986.88	986.72

From the second case of spina bifida the author obtained 500 c.c. of cerebrospinal fluid in the first puncture, and 435 c.c. in the second puncture. The reaction of the fluid in this case was also stated to be alkaline. On boiling, very little, if any, turbidity occurred. On the addition of acetic acid slight flocculency occurred. Quantitative analysis showed the following in grams per 1000:

	FIRST PUNCTURE	SECOND PUNCTURE
Protein	0.25	0.55
Extractives	2.30	2.00
Soluble salts	7.67	7.20
Insoluble salts	0.45	0.45
Dry Substance	10.67	10.20

One case of hydrocephalus in a five-month-old girl gave Hoppe the following in grams per 1000: protein 0.70, extractives 1.57, soluble salts 7.67, insoluble salts 0.53, giving dry substance 10.47.

Another case of hydrocephalus gave Hoppe the following in grams per 1000: protein 11.79, alcohol extractives 0.84, water extract 0.48, soluble salts 7.54, insoluble salts 0.35, and dry matter 20.99. However, from the author's description of the fluid of the last case, which he says was of a greenish yellow color and showed a large sediment, absence of sugar and numerous cells, it is evident that the case was one of meningitis.

Halliburton also was one of the first to study the chemical composition of cerebrospinal fluid. He found no coag-

ulation of the fluid at 56° C. and no fibrin on the addition of serum or fibrin ferment. He found further that practically all the protein present in the cerebrospinal fluid was precipitated by saturation with magnesium sulphate. The analysis of cerebrospinal fluid in a number of cases gave Halliburton the following results in parts per 1000:

	CASE 1. FEMALE—AGE 19	CASE 2. CHILD—AGE 11 DAYS FIRST TAPPING	CASE 3. CHILD—AGE 13 WEEKS FOURTH TAPPING
Water	989.75	989.877	991.658
Solids	10.25	10.123	8.342
Proteins	0.842	0.602	0.199
Extractives and Salts	9.626	0.631 7.890	3.028 5.115

Recent Investigations

Some of the earlier work has been corroborated and a number of new facts have been obtained recently in connection with the chemical composition of cerebrospinal fluid. I shall discuss here only the most important chemical constituents of the fluid. Unless otherwise indicated, the figures are for fluid obtained by lumbar puncture.

INORGANIC CONSTITUENTS

Total Solids

Mestrezat found the total solids of normal cerebrospinal fluid to vary between 1.065 and 1.100 gm. per 100 c.c. of fluid. Various other authors found the total solids to vary between 1.200 and 0.876 gm. per 100 c.c. The specimens I examined contained between 1.398 and 1.631 gm. of total solids per 100 c.c. of fluid, the water varying between 98.602 and 98.369 gm. per 100 c.c. I should like to point out once more that I prefer to speak of nonmeningitic and nonluetic fluid rather than of normal fluid, as I believe that very few fluids brought to any laboratory are normal.

Calcium

The calcium content of the cerebrospinal fluid has been variously given. (Table XII.)

TABLE XII

AUTHOR	MG. OF CALCIUM IN 100 C.C.		% RATIO C.S.F. Ca / SERUM Ca
	CEREBROSPINAL FLUID	BLOOD SERUM	
Yvon	11.2		
Mestrezat	9.5		
Halverson and Bergheim	5.0		
Kummer and Minkoff	5-5.2		
Leichner	5.2	11.3	46%
Depisch and Richter-Quittner	2.5		
Neustaedter, Hala and Tolstoouchow	5.52		
Barrio	4.6-6.0		
Weston and Howard	5.2-5.4	10.4-10.6	50%
Critchley and O'Flynn	6.2		appr. 70%
Osnato, Killian, Garcia and Mattice	5.68	10.94	51%

The calcium content of the cerebrospinal fluid, according to Critchley and O'Flynn, bears no relationship to the fluid pressure, cytology or protein content, or to the calcium content of the blood serum. They point out the necessity of doing the examinations on fluids obtained during life since there occurs a rapid and marked increase in the calcium content of the cerebrospinal fluid postmortem. An interesting relationship between the withdrawal of cerebrospinal fluid and the calcium content of the blood serum has been pointed out by several workers. They found that following the removal of cerebrospinal fluid, there was a rise in the blood calcium. A similar rise occurring following the injection of an extract of the pituitary gland has led Cohen to the assumption that the withdrawal of cerebrospinal fluid causes a release into the fluid of the pituitary secretion, which is then absorbed by the blood. Jacobson's work on the haemodynamic reactions of the cerebrospinal fluid, however, indicates that the pituitary substance is not secreted into the cerebrospinal fluid. Behrendt, in 1923,

estimated that 20 per cent of the calcium in the cerebrospinal fluid is in the ionized form, and that secondary phosphates and bicarbonate ions inhibit the calcium dissociation.

Magnesium

Table XIII shows the results of several workers on the magnesium content of the cerebrospinal fluid, compared with that of the blood. Of these investigations, the work of Cohen is most exhaustive.

Table XIII

AUTHOR	MG. MAGNESIUM IN 100 C.C.		C.S.F. MAGNESIUM / SERUM MAGNESIUM
	CEREBROSPINAL FLUID	BLOOD SERUM	
Mestrezat	3.0-5.0	4.4	68%
Weston and Howard	2.4-2.5	2.4	100%
Barrio (in lues)	1.4-6.1		125%
Cohen	3.28		125%

According to Barrio's and Cohen's findings, the magnesium content of the cerebrospinal fluid per 100 c.c., is greater than that of blood. Cohen states that the magnesium and the chlorides are the only substances present in greater quantities in the cerebrospinal fluid than in the blood. The magnesium content of the cerebrospinal fluid is independent of the age or sex of the patient, the cell count, protein content and Wassermann reaction of the cerebrospinal fluid. Following the subcutaneous injection of magnesium sulphate, Cohen found no rise in cerebrospinal fluid magnesium in six hours, although a blood magnesium rise in the serum occurred within two hours. Weston and Howard found no difference in the magnesium, calcium, sodium and potassium contents of the cerebrospinal fluid in the depressive and in the maniacal stages of manic-depressive insanity. Depisch and Richter-Quittner found no magnesium in normal cerebrospinal fluid. Postmortem, Cohen found a rise in the magnesium content of the cerebrospinal fluid.

Sodium and Potassium

In Table XIV are shown the various figures given for the sodium and potassium contents of the cerebrospinal fluid and the blood.

TABLE XIV

AUTHOR	MG. Na IN 100 C.C.		MG. K IN 100 C.C.		% RATIO C.S.F./BLOOD	
	C.S.F.	BLOOD	C.S.F	BLOOD	Na	K
Mestrezat	323	255	20.8		130%	
Myers			19.2			
McVicar and Ross	382	365	10.5	20.7	104%	49%
Weston and Howard	328-333	330-332	12.7	21.9	100%	58%
Kramer and Tisdall		337		18-21		

AUTHOR	RATIO OF Na TO K	
	IN C.S.F.	IN BLOOD
Mestrezat	15.5:1	
McVicar and Ross	36.4:1	17.6:1
Eskuchen	31.5:1	17.0:1
Weston and Howard	26.1:1	15.1:1

The increase of the Na:K ratio in cerebrospinal fluid over that in the blood is due to the fact that chlorides in the cerebrospinal fluid are mainly in the form of NaCl. The Na is present in the cerebrospinal fluid in about the same concentration as in the plasma. The K is present in cerebrospinal fluid in a little over one-half its concentration in the plasma.

Chlorides

There has been a greater uniformity in the results of various workers upon the chloride content of the cerebrospinal fluid, than upon its other chemical constituents (Tables XV and XVI).

The chlorides are the substances normally present in greater quantity in the cerebrospinal fluid than in the blood plasma. Normal blood plasma values range between 570 and 620 mg. per 100 c.c. The reason for this is unknown. It has been suggested by Mestrezat and also by Depisch and Richter-Quittner that the higher chloride content of

TABLE XV

CHLORIDES IN NONMENINGITIC FLUID

NO.	DIAGNOSIS	CHLORIDES (IN GM. PER 100 C.C.)
1	Psychosis	0.74
2	Alcoholic psychosis	0.72
3	Alcoholic psychosis	0.60
4	Meningism	0.72
5	Pneumonia	0.60
6	Psychosis	0.68
7	Psychosis	0.70
8	Tertiary lues	0.75
9	Chorea	0.70

the cerebrospinal fluid is associated with its lower protein and colloid content, the high chloride content giving the cerebrospinal fluid an osmotic pressure equivalent to that

TABLE XVI

AUTHOR	MG. CHLORIDES IN 100 C.C. CEREBROSPINAL FLUID
Mestrezat	725-740
Freemont-Smith and Dailey	720-750
Eskuchen	725-750
Steiner and Beck	680-720
Levinson	600-750

of the plasma. The decrease in chloride content of the cerebrospinal fluid in meningitis is interpreted, according to this opinion, as being a result of the increase of the protein in these conditions. However, it does not explain why this decrease is greater in tuberculous meningitis, than in purulent meningitis or in Froin's syndrome, in which two conditions the protein increase is greater than in tuberculous meningitis.

Inorganic Phosphorus

Brain tissue has a high phosphorus content. This fact has stimulated the investigation of the phosphorus content of cerebrospinal fluid, as a possible indication of brain tissue changes. Table XVII gives the figures for normal cerebrospinal fluid.

TABLE XVII

AUTHOR	MG. INORGANIC PHOSPHORUS IN 100 C.C. CEREBROSPINAL FLUID
Osnato et al.	1.59
Mestrezat	3.0
Donath	5.4
Cohen	1.5-2.0
Levinson	4.1

Osnato, Killian, Garcia and Mattice working on cerebrospinal fluid and blood serum obtained from epileptic patients, found that the inorganic phosphorus content of the cerebrospinal fluid was about 45 per cent of that of the blood. Cohen states that the inorganic phosphorus content of the cerebrospinal fluid is independent of the phosphorus content of the plasma, the age of the patient, the proximity to death, the cell count or protein content of the cerebrospinal fluid, previous lumbar punctures and bacterial activity. Postmortem, the inorganic phosphorus content of the cerebrospinal fluid rises rapidly. Cohen found 5.41 mg. in 100 c.c. of cerebrospinal fluid removed three hours after death. He attributes the high values for choline in cerebrospinal fluid, as given by Halliburton, Mott, and Donath to the fact that these workers used fluids obtained after death.

Other Inorganic Substances

Mestrezat made a complete analysis of the ash of normal cerebrospinal fluid. He found the total ash to vary between 850 - 900 mg. per 100 c.c. Iron oxide averaged 0.2 mg., nitrates 0.9 mg. and sulphates 1.0 mg. per 100 c.c. Depisch and Richter-Quittner found no iron and aluminum in normal cerebrospinal fluid. The carbonates, in my work, varied with the time the fluid had been standing after removal from the body. The longer it stood before examination, the less CO_2 it contained. In fluid examined immediately after withdrawal from the body, the CO_2 varied between 0.110 gm. and 0.124 gm. per 100 c.c. In fluid examined five to six hours after it had been removed

from the body, the CO_2 varied between 0.098 gm. and 0.106 gm. per 100 c.c. Table XVIII shows the amount of CO_2 in volume per cent obtained in some fluids. It is evident from the table that the P_H and the carbonate content of the cerebrospinal fluid vary inversely as each other.

TABLE XVIII

TOTAL CARBONATE OF NONMENINGITIC CEREBROSPINAL FLUID AND ITS RELATION TO THE H-ION CONCENTRATION

NO.	DIAGNOSIS	PH	TOTAL CARBONATE IN VOLUME PER CENT
1	Dementia Precox	7.4	58.75
2	Psychosis	7.4	55.72
"	"	7.7	51.52
3	Cerebrospinal Lues	7.5	55.72
"	"	7.6	54.83
4	Psychosis	7.4	57.54
"	"	8.1	50.47
5	Tabes	7.4	63.68
"	"	8.1	54.08
6	Chorea	7.5-7.6	63.0
"	"	8.1	52.48
7	Encephalitis	7.7	51.3

ORGANIC CONSTITUENTS

The organic constituents of cerebrospinal fluid attracted the attention of investigators even earlier than did the inorganic constituents. Among the subjects investigated were the total amount of organic matter, the organic or permanganate index, the amount of protein, the type of protein, the amount of urea, amino acids, sugar and cholesterol. Of late, the nitrogen constituents of cerebrospinal fluid have received considerable attention. The subject includes total nitrogen, nonprotein nitrogen, urea nitrogen, and creatinine nitrogen.

Organic Matter and Organic Index

The total organic matter of cerebrospinal fluid varied in Mestrezat's cases between 175 and 265 mg. per 100 c.c. In Hoffman and Schwartz's cases, the organic, reduction

or permanganate index as determined by the Meyerhofer method (described in detail in Chapter XIII) was below 2.0 for normal cerebrospinal fluid. It varied in my cases between 1.3 and 1.8 in the first tube and between 1.1 and 1.7 in the second tube as is evident from Table XIX. The first portion of fluid withdrawn contains more organic matter than subsequent portions.

TABLE XIX

THE PERMANGANATE INDEX IN NONMENINGITIC FLUID

NO.	DIAGNOSIS	PERMANGANATE INDEX		
		FIRST TUBE	SUBSEQUENT TUBES	
1	Typhoid	1.8	1.6	1.7
2	Pneumonia	1.3	1.3	
3	Pneumonia	1.4	1.2	1.0
4	Tetany	1.3	1.2	
5	Epilepsy	1.3	1.1	
6	Grippe	1.5	1.4	

Total Protein

The question of the type of protein in normal fluid is not settled yet. The early investigators claimed that albumin is entirely absent from normal fluid. Mestrezat found that although globulin is the predominant constituent of the protein in cerebrospinal fluid, serum albumin is also pres-

TABLE XX

AUTHOR	MG. OF TOTAL PROTEIN PER 100 C.C. CEREBROSPINAL FLUID
Mestrezat	13.0-30
Ayer and Foster	16.0-38
Eskuchen	20.0-30
Stanford	13.2-25
Levinson	13.0-47
Other authors	16.0-70

ent in normal fluid. In one case he found that the globulin was 13 mg. and the albumin 4 mg. per 100 c.c.

Kirschenbaum and I, using the Howe method for the determination of the distribution of protein in cerebro-

spinal fluid, found no albumin present in normal or nonmeningitic and nonluetic fluids. The only exception to this was found in fluids from two cases of epilepsy, where small amounts of albumin were present. In Table XX, the figures are for the total protein, regardless of the type.

Nitrogen

Table XXI indicates the quantitative distribution of the nitrogenous elements of the cerebrospinal fluid, according to various investigators.

TABLE XXI

AUTHOR	MG. IN 100 C.C. C.S.F. OF				
	TOTAL N	NPN	UREA N	URIC ACID	CREATININE
Mestrezat	19.6-19.8		1.4- 4.7		
Leopold and Bernhard		17.0-26.0	7.0-13.5	Trace	0.7 -1.5
Kahn			14.0-33.0		
Folin			6.0-20.0		
Bernhard				0.3-1.3	
Seham and Nixon					0.45-2.2
Eskuchen			2.8- 9.5		
Cestan, Drouet, and Colombies				0.6-3.6	
Fontecilla and Sepulveda			4.7		
Levinson	21.8-46.4	12.6-38.8	6.0-20.0		0.93-1.4

There has been some confusion in the literature on the figures for urea and uric acid, and on urea nitrogen and uric acid nitrogen. The urea is 2.14 times the urea nitrogen and the uric acid is 3 times the uric acid nitrogen.

Fibrinogen was found by Kirschenbaum and myself to be absent from normal cerebrospinal fluid.

Bernhard found the uric acid content in cerebrospinal fluid of children to be higher than that of adults. The average uric acid content in children's fluid was 0.78 mg. per 100 c.c. while in adults it averaged 0.54 mg. per 100 c.c. Cestan, Drouet and Colombies found the free uric acid of normal cerebrospinal fluid to be constant and about 0.4 mg. per 100 c.c. The combined uric acid was variable in amount, causing the total uric acid to vary between 0.6 and 3.6 mg. per 100 c.c.

Sugar

As early as 1852, Deschambs and Bussy described the presence of a copper-reducing substance in cerebrospinal fluid. This was soon corroborated by numerous other workers. However, the character of this substance has been made the subject of a great deal of discussion. Quincke, Comba, Friedenthal, Panzer and others considered it a dextrose. Halliburton, however, supported by Mathien, Gauthies and others, expressed the view that the reducing substance was pyrocatechin. Langstein thought that a portion of the reducing substance was galactose and Dubos believed that it was a xanthine body. Recent investigations have settled this controversy, the phenylhydrazin, the fermentation test, and the polariscope definitely proving its identity as a dextrose. Halliburton also admits that this reducing substance is a dextrose.

The data on the amount of sugar in cerebrospinal fluid are quite numerous.

Table XXII is taken from Craig and represents the work done on the subject prior to 1924. In my earliest work on

Table XXII

AUTHOR	MG. GLUCOSE PER 100 C.C. CEREBROSPINAL FLUID
Nawratzki	55.5
Mestrezat	48- 53
Kopetzky	46.0
Hopkins	64- 90
Kraus and Corneille	55-110
Schloss and Schroeder	54-139
Scham and Nixon	64- 90
Von Jaksch	60- 80
Levinson	64- 90
Fontecilla and Sepulveda	50.0
Martin	44- 56
Alpers, Campbell and Prentiss	53- 84

cerebrospinal fluid, my figures for sugar were quite high. I found fluids containing over 100 mg. of sugar per 100 c.c. of fluid. In 1925, I repeated a series of nonmeningitic cerebrospinal fluids for sugar content. In this series I

found the sugar content to vary between 50 and 76 mg. per 100 c.c. (Table XXIII). Although the sugar content of cerebrospinal fluid is usually less than 80 mg. per 100 c.c. I believe that anything up to 100 c.c. of fluid should be considered normal.

TABLE XXIII

AMOUNT OF SUGAR IN BLOOD AND CEREBROSPINAL FLUID IN NONMENINGITIC PATIENTS

DIAGNOSIS	BLOOD SUGAR MG. PER 100 C.C.	CEREBROSPINAL FLUID SUGAR, MG. PER 100 C.C.	PERCENTAGE RELATIONSHIP OF CEREBROSPINAL SUGAR TO BLOOD SUGAR
Acidosis	110	67	61
Endocarditis	102	66	64
Trichinosis	78	60	75
Poliomyelitis	100	50	50
Encephalitis	105	69	66
Same case	120	76	63
Same case	91	57	63
Tetany	174	61	35
Brain abscess	114	73	64
Same case	97	50	51
Same case	115	74	65

The amount of sugar in the cerebrospinal fluid in my series bore no relation to the blood sugar. For instance, in a case of tetany with a blood sugar of 174 mg., the cerebrospinal fluid sugar was only 61 mg., or 35 per cent of the blood sugar, and in a case of trichinosis with a blood sugar of 78 mg., the cerebrospinal fluid sugar was 60 mg., or 75 per cent of the blood sugar. This would speak against the contention of Goodwin and Shelley "that there is a definite relationship between the cerebrospinal fluid sugar and the blood sugar, and that the figure representing this relationship, stated as the percental relationship between the two, is relatively constant, lying between 45 and 65 per cent, provided determinations are made on both blood and cerebrospinal fluid taken at the same time, after a night's fasting." This would also speak against the statement of Wilcox and Lyttle, that "normally the spinal fluid sugar concentration is about one-half that of the blood, and that its range of variation corresponds to that of the blood."

Cholesterol

TABLE XXIV

AUTHOR	CHOLESTEROL IN 100 C.C.	
	CEREBROSPINAL FLUID	BLOOD SERUM
Pighini	0	
Mott	0	
Tsuchiya	0	100-230
Mestrezat	trace	150-275
Weston	0.3-0.5	
Osnato, Killian, Garcia, and Mattice	trace	125-171
Levinson	0	

As is evident from Table XXIV, cholesterol is absent from normal fluid, or present only in traces.

Lactic Acid

TABLE XXV

AUTHOR	MG. OF LACTIC ACID IN 100 C.C.		PER CENT
	CEREBROSPINAL FLUID	BLOOD SERUM	
Killian	8.0-15.0	11-15	80-90
Glaser	11-27 (19 av.)	13-45 (23 av.)	75
Osnato and Killian	6.3- 9.4		
Scheller	9.0-15.0		

The lactic acid content of the cerebrospinal fluid is thus seen to be about 75% that of the blood under normal conditions.

Cholin

Cholin is present in normal cerebrospinal fluid in minute quantities. Halliburton and Mott considered the presence of choline in the cerebrospinal fluid as evidence of nervous activity. Gumprecht and Kopetzky believe that it comes from decomposition of lecithin. As mentioned above, the choline content of cerebrospinal fluid becomes rapidly increased postmortem.

Organic Phosphorus

Youngburg, working on fluids taken from patients suffering from syphilis, meningitis and also on nonmeningitic and nonluetic fluids, found the organic phosphorus to vary

between 0.1 – 0.3 mg. per 100 c.c. He found no relation between the organic phosphorus content and the inorganic phosphorus content of the cerebrospinal fluid, or the type of pathology present. He concludes that the amount of organic phosphorus present could not be used as an index of nerve tissue destruction. The organic phosphorus is not in combination with lipoids but with proteins, he believes. Postmortem, the change in organic phosphorus content, according to him, is very slow.

Urobilin and Bilirubin

Eskuchen and Fontecilla and Sepulveda found no urobilin or bilirubin in normal cerebrospinal fluid, even in severe cases of icterus. I found no urobilin or bilirubin in normal cases. However, in severe jaundice, I have occasionally found bile pigments in the cerebrospinal fluid.

Other Organic Constituents

Mestrezat and Halliburton found traces of lecithin in cerebrospinal fluid. Acetone and acetic acid are normally absent from cerebrospinal fluid. Various authors have stated that amino acids are present in quantities varying from 1 to 4 mg. per 100 c.c. Osnato, Killian, Garcia and Mattice found the total phenol content of the cerebrospinal fluid to be 0.69 mg., compared to 1.8 mg. per 100 c.c. in the blood.

The chemical methods that have been found of diagnostic value will be described in detail in Chapter XIII. The methods employed for research purposes are the same as those employed for blood, a detailed description of them being found in the various textbooks on physiologic chemistry.

Comparison of Cerebrospinal Fluid and Blood Chemistry

Deductions as to the nature and origin of the cerebrospinal fluid must depend in a great measure on compara-

tive studies of cerebrospinal fluid and other body fluids, notably blood, lymph, and aqueous humor of the eye. Of these, the relation of the cerebrospinal fluid to the blood has received the most attention. Cerebrospinal fluid and blood contain practically the same constituents, but in different concentrations. The chlorides and, according to Cohen, the magnesium also, are the only substances which the cerebrospinal fluid contains in appreciably greater quantities than the blood. Even in the meningitides, where the cerebrospinal fluid chlorides are reduced, they are never reduced below the level of the blood chlorides.

The sodium content of the cerebrospinal fluid is usually the same or slightly higher than that of the blood. However, the potassium content of the cerebrospinal fluid is only about one-half that of the blood. It follows that the ratio of sodium to potassium in the cerebrospinal fluid is approximately twice that of the blood.

Critchley and O'Flynn noted that the calcium content of the cerebrospinal fluid, while only 50 to 70 per cent of that of the blood was equal to approximately 100 per cent of the blood content of ionized calcium. They found a greater decrease in blood calcium than in cerebrospinal fluid calcium in tetany and explain this on their finding of a greater degree of ionization of calcium (95 per cent) in the blood of patients having tetany.

The other inorganic constituents of the cerebrospinal fluid are present in roughly one-half their concentration in the blood. Pincus and Kramer determined the concentrations of anions and cations in normal serum and cerebrospinal fluid to be, in mg. per 100 c.c., as shown in Table XXVI.

The blood contains much more protein than does the cerebrospinal fluid which accounts for its higher specific gravity. Normally only very small amounts of protein are present in cerebrospinal fluid and these are mainly globulins. Often we find that the blood and cerebrospinal fluid contain practically the same amounts of certain organic constituents. This is particularly true of nonprotein nitro-

TABLE XXVI

Material	Ca	P	Cl(NaCl)	K	Na	CO_2
Serum	9.6	2.9 (adults) 4.6 (children)	578	20.9	328	55.6
Cerebrospinal fluid	4.6	1.3	712	14.7	351	55.7

In terms of gram-molecules per liter this would be:

	Na	P	Ca	Cl	$2(CO_3)$	PO_3	TOTAL	
							AN-IONS	CAT-IONS
Serum	0.143	0.005	0.0025	0.102	0.032	0.001	0.135	0.150
Cerebrospinal fluid	0.143	0.004	0.0012	0.124	0.32	0.0006	0.157	0.148

gen, urea and sugar. I have found nonprotein nitrogen and sugar to be present in the same amounts in both the fluid and the blood. Cullen and Ellis found a difference of less than 2 mg. per 1,000 c.c. in the amounts of urea in the fluid and the blood, in 63 per cent of their determinations. The urea content of the fluid varied from 22 to 46 mg. and that of the blood serum between 20 and 42 mg. per 100 c.c. in their cases. In general, however, the NPN, urea, uric acid, creatinine, sugar and lactic acid of the cerebrospinal fluid vary from 50 to 95 per cent of their concentrations in the blood.

Cholesterol, acetone, diacetic acid, choline and lecithin are normally absent from cerebrospinal fluid or present only in traces.

Of the many defensive properties in the blood, practically none are transmitted to the cerebrospinal fluid. Thus, the cerebrospinal fluid is devoid of antitoxins, opsonins, alexins, bacteriolysins, etc. In this respect cerebrospinal fluid resembles the other fluids in body cavities; e.g., the pleural, pericardial and synovial fluids. In lues of the central nervous system, however, it frequently occurs that the cerebrospinal fluid gives a positive Wassermann while the blood is Wassermann negative. The presence in the cerebrospinal fluid of the "reagin" of syphilis is explained by Kolmer on the hypothesis that it is formed in the central nervous system by the action of the spirochete on nervous tissue.

The P_H and alkali reserve of the cerebrospinal fluid and of the blood serum are practically identical.

Mestrezat was the first to point out the similarity between the aqueous humor of the eye and the cerebrospinal fluid both in point of origin, absorption and composition. Freemont-Smith and Eskuchen have again emphasized this point. In fact the cerebrospinal fluid closely resembles in composition all the protein free blood filtrates of the body such as, edema fluids, transudates and the urine in the Bowmans capsules of the nephron, before water absorption has occurred in the tubules. This similarity points to the cerebrospinal fluid as being an ultrafiltrate of the blood rather than a secretion.

TABLE XXVII

COMPARISON OF THE CHEMICAL AND PHYSICOCHEMICAL COMPOSITION OF BLOOD SERUM AND CEREBROSPINAL FLUID
(Expressed in mg. per 100 c.c.)

	BLOOD		CEREBROSPINAL FLUID	
Water	90880	92000	98300	99660
Dry matter	9110		1630	1090
Organic matter	8250		175	265
Protein	6700	8700	13	47
Total nitrogen	2650		19.6	46.4
Nonprotein nitrogen	20	40	12.6	38.8
Urea nitrogen	12	20	1.4	20.0
Uric acid	2	4	0.3	3.6
Creatinine	1	2.2	0.45	2.2
Amino acids	4	8	1.0	4.0
Sugar	80	120	50.0	100.0
Cholesterol	150	275	0.0	Trace
Lactic acid	11	15	8.0	15.0
Chlorides (as NaCl)	560	650	600.0	750.0
Sodium	343		323.0	382.0
Potassium	18	21.9	10.5	20.8
Sodium: Potassium	15.1:1	17.6:1	15.5:1	36.4:1
Calcium	9	11	4.6	9.5
Magnesium	2	4	2.4	5.0
Iron	56	58	0.2	
Nitrate			0.9	
Sulphate	13		1.0	
Phosphorus (inorganic)	3.7		1.5	5.4
Phosphorus (organic)			0.1-	0.3
Specific gravity	1.040	1.065	1.0034	1.0070
Freezing point	−0.56°C.		−0.56°C.	−0.58°C.
H-ion concentration	P_H 7.4	7.6	7.4	7.6
Alkali reserve	45-	63%	45-	63%
Viscosity	1.8	2.1	1.04	1.09
Refractometric index	1.3487	1.3517	1.33472	1.33545

Table XXVIII

Inorganic Constituents of Cerebrospinal Fluid (in Mg. per 100 c.c.)

Author	Water	Total Solids	Calcium	Magnesium	Sodium	Potassium	Ratio of Sodium to Potassium	Iron (as oxide)	Chlorides	Inorganic Phosphorus	Sulphates	Nitrates	Carbonates	Total Ash
Mestrezat	98,900 to 98,935	1,065 to 1,100	9.5	3 to 5	323	20.8	15.5:1	0.2	728 to 740	3	1.0	0.9		850 to 900
Zdarek	98.955	1.045.2			318	13.7								835.6
Polanyi	98,330 to 98.855	1,045 to 1,070			305 to 356									919 to 950
Yvon			11.2											
Halverson and Bergheim			5.0											
Kummer and Minkoff			5.0 to 5.2											
Leichner			5.2											
Depisch and Richter-Quittner			2.5	0										
Neustaedter et al			5.52											
Barrio			4.6 to 6.0	1.4 to 6.1										
Weston and Howard			5.2 to 5.4	2.4 to 2.5	328 to 333	12.7	26.1:1							
Critchley and O'Flynn			6.2											
Osnato et al			5.68							1.59				
Myers						19.2								
McVicar and Ross					382	10.5	36.4:1							
Eskuchen							31.5:1		725 to 750					
Freemont-Smith and Dailey									720 to 750					
Steiner and Beck									680 to 720					
Donath										5.4				
Cohen				3.28										
Levinson	98,369 to 98,602	1,398 to 1,631							600 to 740	4.1			110 to 124	920

Table XXIX

Organic Constituents of Cerebrospinal Fluid

(in Mg. per 100 c.c.)

Author	Total Organic Matter	Permanganate Index	Total Protein	Total N	N. P. N.	Urea N	Uric Acid	Creatinine	Sugar	Cholesterol	Lactic Acid	Organic Phosphorus	Amino Acids	Choline	Lecithin
Mestrezat	175 to 265		13 to 30	19.6 to 19.8		1.4 to 4.7			48 to 53	tr.			1		
Zdarek	209.6		76.8												
Hoffman and Schwartz		below 2													
Ayer and Foster			16 to 38												
Eskuchen			20 to 30												
Stanford			13.2 to 25			2.8 to 9.5									
Leopold and Bernhard					17 to 26	7 to 13.5	tr.	0.7 to 1.5							
Kahn						14 to 33									
Folin						6 to 20									
Fontecilla and Sepulveda						4.7			50						
Seham and Nixon								0.45 to 2.2	64 to 90						
Bernhard							0.3 to 1.3								
Cestan, Drouet and Colombies							0.6 to 3.6								
Nawratzki									55.5						
Kopetzky									46						
Hopkins									64 to 90						

TABLE XXIX—CONT'D

ORGANIC CONSTITUENTS OF CEREBROSPINAL FLUID

(in Mg. per 100 c.c.)

AUTHOR	TOTAL ORGANIC MATTER	PERMANGANATE INDEX	TOTAL PROTEIN	TOTAL N	N. P. N.	UREA N	URIC ACID	CREATININE	SUGAR	CHOLESTEROL	LACTIC ACID	ORGANIC PHOSPHORUS	AMINO ACIDS	CHOLINE	LECITHIN
Kraus and Corneille									55 to 110						
Schloss and Schroeder									54 to 139						
Von Jaksch									60 to 80						
Martin									44 to 56						
Alpers, Campbell and Prentiss									54 to 84						
Pighini										0					
Weston										3.5					
Killian											8 to 15				
Glaser											11 to 27				
Osnato and Killian											6.3 to 9.4				
Scheller											9 to 15				
Youngburg												0.1 to 0.3			
Halliburton														tr.	
Mott														tr.	
Levinson		1.0 to 1.8	13 to 47	21.8 to 46.4	12.6 to 38.8	6 to 20		0.93 to 1.4	46 to 95	0					tr.

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CHAPTER VII

NORMAL CEREBROSPINAL FLUID BIOCHEMICAL PROPERTIES AND CYTOLOGY

The data on the biochemical properties of normal cerebrospinal fluid are conflicting in nature. Up to date most of the biochemical properties reported on have been negative in nature, but it is possible that with more accurate methods positive biochemical properties may be found.

Catalase

In a series of fluids examined by Becht and myself, by means of a special apparatus described by Becht, no catalase or only a negligible amount was found in normal cerebrospinal fluid. (Table XXX.)

Table XXX

Catalase in Nonmeningitic Fluid

DIAGNOSIS	INTERVAL	READING	CELLS PER C.MM. AT TIME OF DETERMINATION OF CATALASE	OTHER TESTS
Chorea	½ hr.	0, 0	4	0
Microcephalus	½ hr.	0, 0	4	0
Meningism	2 days	2, 2	2	Globulin slightly positive
Normal	2 days	3, 2, 2	4	0
Scarlet fever and diphtheria	4 days	5, 5	0	0
Epilepsy	1½ hr.	2, 2, 2	1	0
Brain tumor	1 hr.	4, 4, 4, 4	50 lymphocytes	0
Cerebral hemorrhage	19 hr.	2, 2	2	Globulin positive

Amylase

Toison and Lenoble found that the cerebrospinal fluid of hydrocephalics possesses amylolytic power. Cavazzani

reports the same. Galletta, however, found this to be true in only two out of eleven cases examined. Mestrezat found no amylolytic power in normal cerebrospinal fluid or very slight traces of it.

Oxidase

Normal fluid contains oxidases in small quantities.

Diastase

Diastase is present in small quantities according to Eskuchen.

Proteolase

Link and Pollack report finding a peptolytic enzyme in normal cerebrospinal fluid. In three cases of hydrocephalus and one case of spina bifida examined for the presence of pepsin or trypsin Halliburton found no trace of either. Miller found no proteolytic enzyme or antienzyme in normal cerebrospinal fluid.

Lipase

Galletta found a fat-splitting enzyme in three of seven cases. Clerc found none.

Glycolytic Ferment

Cavazzani found glycolytic ferment in the cerebrospinal fluid. However, neither Panzar, Lewandowsky, nor Mott could find the presence of any glycolytic ferment.

Opsonin

Normal fluid contains no opsonin or only traces of it.

Alexin

Normal fluid contains no alexin.

Hemolysin

Normally no hemolysin is found in the fluid.

Toxicity

Normal fluid is not toxic, compared to pathologic fluid which is toxic.

Antitoxins

Normal fluid contains no antitoxins.

Bactericidal Action

The question as to whether normal fluid has a bactericidal action has not yet been settled. Kolmer found no agglutinins or bacteriolysins in the cerebrospinal fluid of patients whose serum was immune to typhoid and other bacilli.

CYTOLOGY

The study of the cell content and of the cell elements of the cerebrospinal fluid was inaugurated in France by Ravaut, Sicard, Nagoette and Widal in 1901, and has since been recognized as a very important phase of the study of the cerebrospinal fluid.

The exact number of cells in normal cerebrospinal fluid is a matter on which authorities who have worked with the fluid do not agree. Fuchs and Rosenthal found 0 to 2 cells per c.mm. in normal fluid, Rehm found 1 to 5 and even 6 to 9, and Gennerich found 8 cells in the fluid of one healthy person. There are others who give the number as 5 to 20 per c.mm. The reason for the wide discrepancy is the fact that different investigators have employed different methods in determining the number of cells. There are some who count the cells in the centrifuged fluid, using a certain amount of fluid in a graduated centrifuge tube and taking one drop of the sediment on a slide (the so-called French method), and others who count the cells of uncentrifuged fluid, in counting chambers. It is easy to see how these two methods will give entirely different results, the difference being at times as high as 50 or 60 per cent. Even

those who count the cells in a counting chamber, get variations in their results due to the type of chamber they use. The Fuchs-Rosenthal chamber, for instance, gives a smaller percentage of error than the ordinary leucocyte counter. Another source of error is the disagreement as to what to call a normal fluid. The greatest source of errors responsible for the discrepancy in results of various authors however, is the admixture of blood in the cerebrospinal fluid, for no matter how clear the fluid may look there may be some blood cells obtained by the passage of the needle through the tissue, which would in turn result in enormous errors, when figured out as their number per c.mm. In addition to the above factors, diluting fluid may account for the difference in the reports of the various authors.

I found the number of cells in normal fluid to be between 1 and 6 per c.mm. I have, therefore, adopted this number as an arbitrary standard, anything above 6 cells per c.mm. being suspicious, and anything above 10 cells per c.mm. being indicative of some pathologic condition of the central nervous system, although not every increase in cells means an inflammation of the meninges. Some cases showing an increased cell count in the cerebrospinal fluid are due merely to an irritation of the meninges. Of course I make certain that the cerebrospinal fluid contains no blood to begin with.

The cell count of fluid obtained by lumbar puncture is not indicative of the cell count in the cerebrospinal fluid contained in the ventricle of the brain. The ventricular fluid contains fewer cells than the lumbar fluid.

I have found that the cell count varies with the different portions of the cerebrospinal fluid, the fluid in the first portion containing more cells than the subsequent fluid. I believe that this may be due to a contamination of blood cells in the first portion of the fluid. In this connection,

it is interesting to point out that one author advises shaking the patient from side to side before doing a lumbar puncture, in order to stir up the cells and distribute them evenly which, of course, is very absurd.

Type of Cell

Normally, no red blood cells are found in cerebrospinal fluid, the cells always being leucocytes. The normal type of leucocyte in cerebrospinal fluid is the small lymphocyte, which is the size of a red blood cell or slightly smaller or larger than the red blood cell. The nucleus of the lymphocyte of normal cerebrospinal fluid is round or slightly oval. It is seldom irregular. The nucleus fills up the larger part of the cell leaving a very small cytoplasm. No granules can be detected in the cells, as a rule. The nucleus stains intensively with methyl-violet, while the cell body does not.

Large lymphocytes do occur in normal fluid but not very frequently. It has been observed that there very seldom exists a combination of large and small lymphocytes in the same specimen of fluid that gives no other pathologic changes. Large lymphocytes, however, always should make one think of some diseased condition of the central nervous system.

Polymorphonuclear leucocytes are usually absent in normal fluid. Fontecilla and Sepulveda, however, state that normally 5 per cent of the cells are polymorphonuclear leucocytes. It should be kept in mind, however, that one or two polymorphonuclear leucocytes may be present in normal cerebrospinal fluid, from contamination with blood, as may happen even in successful punctures.

The origin of the cells in normal cerebrospinal fluid is not fully determined. They would seem to be of hematogenous origin as they are the same forms normally present in the blood.

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CHAPTER VIII

PATHOLOGIC CEREBROSPINAL FLUID
GENERAL CONSIDERATIONS

Changes in the cerebrospinal fluid are, for the greater part, due to meningeal reaction. The degree of change in the cerebrospinal fluid will therefore vary with the degree of meningeal reaction. The absence of abnormal cerebrospinal fluid findings in many degenerative diseases of the central nervous system may be explained by the absence of a meningeal reaction in these conditions. With this in view, changes in the cerebrospinal fluid may be classified as the results of the following causes:

1. Infection of the meninges.
2. Irritation of the meninges due to
   (a) Chemical substances.
   (b) Toxins.
   (c) Mechanical causes.
   (d) Neoplasms of the meninges.
   (e) Sympathetic response.

In addition to these causes, cerebrospinal fluid changes, independent of meningeal reaction, may also be due to the following conditions:

1. Trauma.
2. Metabolic disturbances.
3. Increase of foreign chemical substances in the blood.

INFECTION OF THE MENINGES

Infection of the meninges may be chronic, as in lues, or acute as in the various acute meningitides. The changes in the fluid due to infection of the meninges are usually physical, chemical, cytologic, bacteriologic and immunologic. The changes may appear singly or in various combinations. They are a reflection of, and correspond to

the changes in the meninges found on postmortem examinations. Thus in meningococcus meningitis endothelial cells are found both in the fluid and in the meninges (Figs. 28 and 29) and in tuberculous meningitis lymphocytes predominate in the fluid and in the meninges (Fig. 30).

The nervous system is the master system of the body, and Nature has provided it with protection by surround-

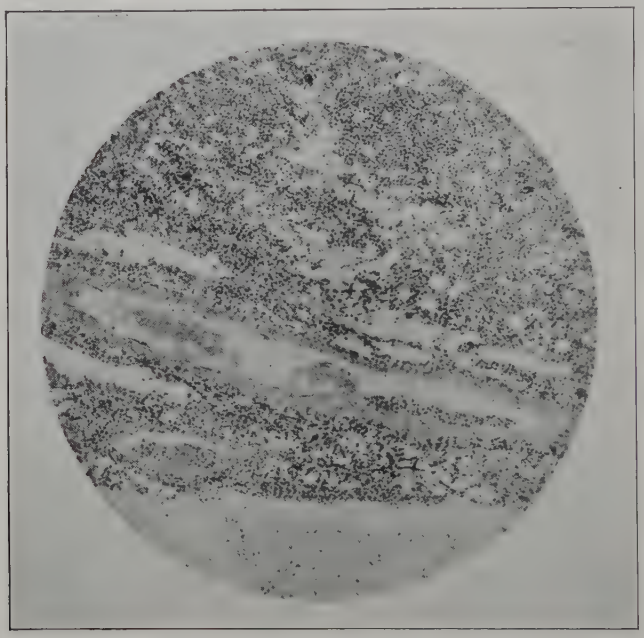

Fig. 28.—Acute meningococcus meningitis. The brain, below, is covered by a thick layer of purulent exudate. Hematoxylin and eosin. X95.

ing it with cerebrospinal fluid and with three layers of meninges, one of which, the dura, is especially heavy and firm. In addition, Nature also protects the meninges with the heavy walls of the skull and spine and in spite of the fact that the nervous system is a delicate system, and that the cerebrospinal fluid is not microbicidal it is not easy for bacteria to gain access to either.

Just how bacteria may enter the cerebrospinal fluid is still a matter of controversy. There are two ways in which

they can make their entrance: one is through the circulation and the other is by direct continuity from the nose or from the ears. For a long time it was thought that the attack on the meninges in meningococcus meningitis was by way of the lymphatics of the nasal mucous membrane, the bacteria passing through the cribriform plate of the ethmoid directly into the meninges. However, the fact

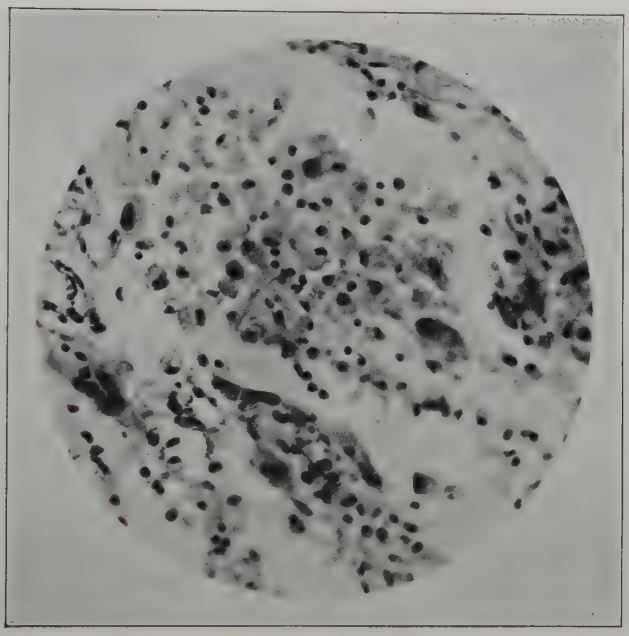

Fig. 29.—Acute meningococcus meningitis. A group of swollen endothelial cells. Hematoxylin and eosin. X300.

that the meningococcus in many cases may be cultivated directly from the blood in the early stages of meningitis, and that arthritis and iridochoroiditis often complicate and even precede meningitis, would make one believe that the meningeal infection is most frequently hematogenous. The recent work of Herrick on meningeal infection in man and of Austrian on experimental meningitis speaks in favor of the septicemic nature of meningococcic invasion.

In tuberculous meningitis the infection hardly ever reaches the meninges directly from the nose. It is usually part of a general miliary tuberculosis of which the meningitis is a terminal process. From the work of Albrecht and Ghon, we know that the primary focus of tuberculosis is usually in the lung, and this gives rise to an enlargement of the hilus glands, which in time either becomes retrogressive with calcification, or leads to a general miliary

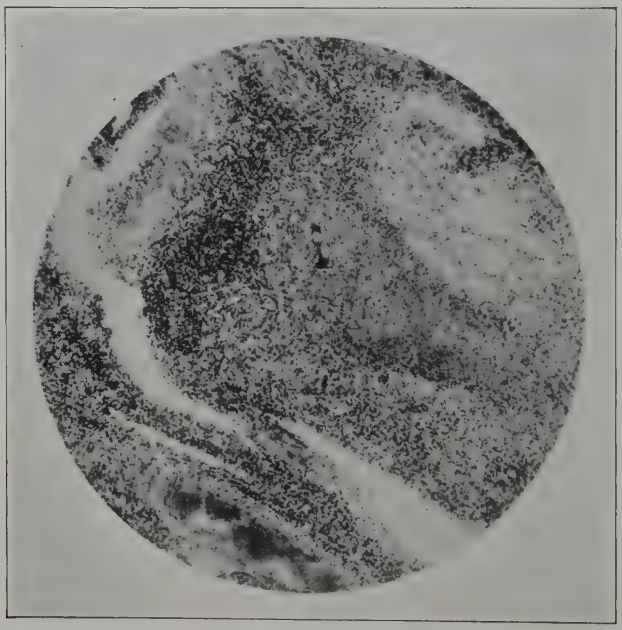

Fig. 30.—Tuberculous meningitis. At the lower margin is an area of caseation necrosis. In the middle is a tubercle with a giant cell. The pia is diffusely infiltrated by lymphocytes. Hematoxylin and eosin. X95.

tuberculosis. According to this explanation, what happens in tuberculous meningitis, then, is first a tuberculous infection in the lung tissue proper; second, an infection of the hilus glands; and third, an invasion of the meninges by way of the blood. It takes some time before the protective wall of the meninges is broken through by the tubercle bacilli, but they finally break through and in-

fect the meninges. That tuberculous meningitis is a part of a miliary tuberculosis is seen on autopsy, miliary tubercles being found in the lungs, liver, and spleen in nearly all such cases.

The pneumococci act much like the tubercle bacilli and meningococci in their relation to meningitis. Not every pneumonia, it is true, produces a pneumococcus meningitis but almost every pneumococcus meningitis is the result of a pneumococcus septicemia. Some observers claim that they have found pneumococci in the cerebrospinal fluid in uncomplicated pneumonia, although there is no apparent reason why pneumococci in the fluid should produce meningitis in one instance and not in another.

In certain cases the meningococci and other bacteria do find their way into the cerebrospinal fluid through the cribriform plates of the ethmoid. The nasal mucous membrane may harbor pneumococci, streptococci, menignococci and influenza bacilli, and it is conceivable that when the system is in a low state of resistance, the bacteria may enter the meninges directly. The cerebrospinal fluid in these cases, instead of being a means of protection for the central nervous system, serves as a good medium for the dissemination of the bacteria.

Still another route for the entrance of bacteria into the cerebrospinal fluid is the ear. In advanced cases of otitis media or mastoiditis, the bacteria may enter the brain substance, in which case they produce a brain abscess with mere irritation or an inflammation of the meninges. They may also directly enter the meninges, in which case they produce a meningitis. This happens most frequently in infections with the pneumococcus, and with the hemolytic streptococcus.

Less frequently bacteria make their way into the cerebrospinal fluid through wounds of the skull and spine, especially through fractures of the skull.

Whichever way the bacteria enter the cerebrospinal fluid, once there, they produce changes in the meninges or

brain and give rise to many alterations in the fluid. Some of the changes are common to all pathologic processes in the meninges or brain, whereas others are specific to certain bacteria or toxic substances.

IRRITATION OF THE MENINGES

Chemical irritation of the meninges occurs in such conditions as a lead encephalitis and meningitis. In this condition, lead may be present in the cerebrospinal fluid.

Toxic irritation of the meninges occurs in some of the acute infectious diseases in which cases there may be the clinical symptoms of meningeal irritation with changes in the cerebrospinal fluid limited to an increase in pressure alone. This particular syndrome is known as meningism; or as others call it, serous meningitis. The pathogenesis of meningism, I believe, may be explained on simple mechanical grounds. If one keeps in mind that the cerebrospinal fluid is greatly influenced by the blood pressure inside of the cranium, it can easily be seen that any irritating substance reaching the brain either by the general circulation, as in pneumonia, or through adjacent structures, as occurs in otitis media, will accelerate the circulation of the blood in the cranium, thus raising the intracranial and consequently the cerebrospinal fluid pressure. At this point, removal of cerebrospinal fluid by lumbar puncture will decrease the intracranial pressure and often cause a subsidence of the meningitic symptoms. Likewise, a diversion of the blood supply to parts of the body other than the cranium will decrease the signs of meningeal irritation. This is probably the explanation of the observation that often in acute infectious diseases associated with meningism, when the infection localizes, the meningeal symptoms disappear. Thus, in pneumonia when the pulmonary findings develop, the transference to the lungs of large quantities of blood from the brain decreases the intracranial pressure and causes the meningeal signs to disappear.

Toxic irritation of the meninges also occurs in those conditions where inflammatory changes occur in the parenchyma of the central nervous system as in encephalitis or brain abscess. The changes that occur in the cerebrospinal fluid in encephalitis are proportional to the degree of meningeal reaction, which is usually demonstrable postmortem by proliferative and degenerative changes in the meninges. The same is generally the case in brain abscess (see Fig.

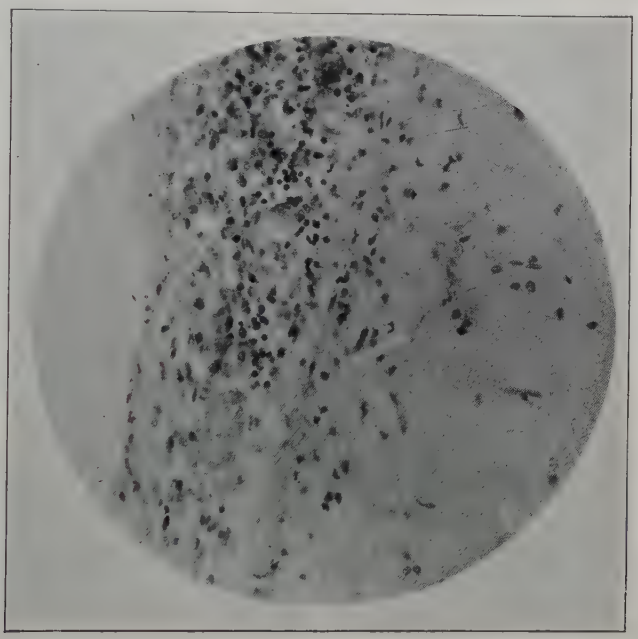

Fig. 31.—Irritation of the pia associated with abscess of the brain. The pia, at the left, is slightly edematous, its nuclei are swollen, and at the upper margin of the picture are a few lymphocytes and a dilated blood vessel. Hematoxylin and eosin. X230.

31). However, since no pathologic process is stationary, irritation of the meninges, if prolonged, may finally lead to inflammatory changes in the meninges, which lead to characteristic meningitic changes in the cerebrospinal fluid and characteristic gross and microscopic pathologic changes in the meninges (see Fig. 32).

In some patients suffering from infectious diseases, there are no symptoms of meningeal irritation such as rigidity of the neck, Kernig, Brudzinski or Babinski signs. There is, however, an accompanying lethargy or other symptoms of brain irritation. In these cases the cerebrospinal fluid may show slight changes or none at all.

Mechanical irritation of the meninges occurs from pressure, due to tumors of the brain or cord, or to depressed

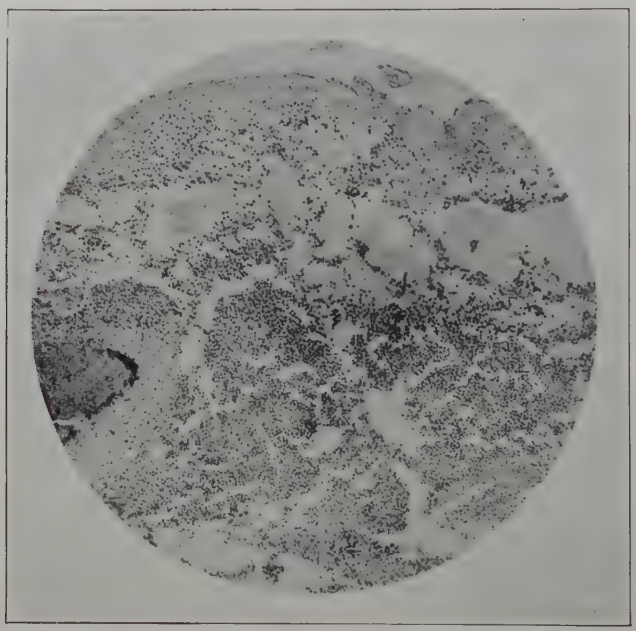

Fig. 32.—Acute purulent meningitis secondary to abscess of the brain. At the left is an artery whose wall is infiltrated by leucocytes. Hematoxylin and eosin. X80.

skull fractures. Under these conditions there may be an increase in the pressure, cell count and globulin content of the cerebrospinal fluid. Following the withdrawal of cerebrospinal fluid there is occasionally mechanical irritation of the meninges followed by a meningeal reaction manifested clinically by headache, stiff neck, etc.

Sympathetic irritation of the meninges occurs in infections of structures adjacent to the meninges; e.g., in acute otitis media or mastoiditis. This condition described in detail by Strauss and called by him "meningitis sympathica," probably has the same pathogenesis as meningism. It differs from meningism in that in meningitis sympathica the changes in the cerebrospinal fluid simulate that of a meningitis, with an increase in cells, globulin, whereas in meningism the main change is an increase in pressure.

TRAUMA AND OTHER FACTORS

Although changes in the cerebrospinal fluid are usually secondary to meningeal changes, there are other causes of cerebrospinal fluid changes independent of meningeal reaction. These causes may be

1. Traumatic.
2. Metabolic.
3. Chemical concentration.

As examples of such traumatic causes are skull fractures and spontaneous intracerebral hemorrhages, in which cases the cerebrospinal fluid contains large quantities of blood.

A metabolic disorder or any pathologic process that increases the concentration in the blood of substances that permeate the normal meninges will cause changes in the cerebrospinal fluid. Thus, in diabetes, the cerebrospinal fluid sugar is increased, even though the meninges are intact. Likewise there is an increase in chlorides and urea in the cerebrospinal fluid in uremia.

Alcohol, hexamethylenamine, chloroform, and several other chemicals, which are normally absent from the blood, are able to permeate the normal meninges. Ingestion of any of these chemicals in sufficient quantities is therefore followed by its appearance in the cerebrospinal fluid, even in the presence of normal meninges.

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CHAPTER IX

PATHOLOGIC CEREBROSPINAL FLUID PHYSICAL AND PHYSICOCHEMICAL PROPERTIES

PHYSICAL CHANGES

Color

In some pathologic conditions the color of the fluid is altered while in others the fluid remains clear and colorless. In most acute suppurative meningitides the fluid is turbid. In meningococcus meningitis the fluid has a yellowish green tinge. In pneumococcus meningitis the fluid is often pearly gray in color. In tuberculous meningitis and poliomyelitis the color of the fluid usually remains unchanged although occasionally the fluid is opaque, and at times yellow. In certain tumors of the dura the cerebrospinal fluid may have a greenish tinge.

In hemorrhage of the brain the fluid is bright red when the hemorrhage is of recent origin and deep yellow when of long standing.

A yellow fluid is also obtained in tumors of the cord and occasionally in chronic meningitis. The term xanthochromia has been used to indicate any yellow discoloration of the fluid. Xanthochromia and massive coagulation is a term used by Froin for a condition in which the fluid is yellow in color and coagulates immediately after withdrawal from the body. This syndrome is present in tumors of the spinal cord.

In marked jaundice the cerebrospinal fluid may have the color of bile.

Increase in Amount of Obtainable Fluid

It is the rule that whenever there is irritation in some serous cavity, the fluid normally present is increased in

amount. This is true of the pleural cavity, the peritoneum, pericardium, and also of the meninges. Any irritation of the meninges, therefore, increases the amount of cerebrospinal fluid, the increase in some cases being only moderate, in others very great. That this occurs is indicated by the increase in pressure and in the increase in the amount of fluid obtainable at a single sitting. Is every case of increased cerebrospinal fluid to be termed a serous meningitis as Quincke proposed? It would seem less confusing to use Dupré's term of meningism for all cases where the fluid shows only physical changes and reserve the term meningitis for all processes producing chemical, cytologic and bacteriologic changes. The name, however, makes little difference. It should be noted that the more acute the irritation, the greater the amount of fluid accumulating in the ventricles and in the subarachnoid spaces.

There are, however, cases in which the amount of fluid obtainable is decreased. This occurs in tumors of the cord.

Pressure

With the increase in the amount of fluid in the subarachnoid space there is naturally an increase in the pressure of the fluid, so that we very seldom have a pathologic process of the meninges without a corresponding increase of the pressure of the fluid. Here also the character of the process and the degree of its acuteness determine the increase in pressure. Occasionally, however, there is a decrease in pressure. This is seen in tumors of the cord with subarachnoid block. This may also be found in brain tumors where there is a blocking of the foramen magnum by the tumor, and in obstructive hydrocephalus due to meningitis. In general, in tumors of the cord, the pressure is increased above and decreased below the site of obstruction.

Foam

I found that all pathologic fluids produce a foam on shaking. When a test tube is filled one-third to one-half its

depth with fluid, and is shaken for two or three minutes, a heavy foam one to two inches in thickness forms, persisting for half an hour or longer. When normal fluid is shaken in a test tube only a thin foam forms, disappearing in a few minutes. The foam is present in all pathologic fluids, but it is of greater size and duration in acute infections of the meninges. Zingher described the formation of a heavy foam in acute poliomyelitis which corroborates my observations. It seems but natural to think that the foam production is due to the CO_2 in the fluid. Close observation, however, does not bear this out. I found repeatedly that a foam formed just as readily in fluid in which all the CO_2 had been driven off, if the fluid was pathologic. The foam, therefore, is best explained by the increased amount of protein in the fluid.

Pellicle, Coagulum or Sediment

In addition to the physical changes which make their appearance in the cerebrospinal fluid under all pathologic conditions of the meninges, such as an increase in the amount, in the pressure, and the foam of the fluid, there is one change which takes place in the cerebrospinal fluid that is fairly characteristic for some diseases. This is the formation of a pellicle or sediment. The absence of a pellicle does not rule out pathology, however.

In most acute diseases of the meninges a pellicle or a net of fibrin and blood cells forms in the fluid on standing. The time it takes a pellicle to form varies with the character of the disease. In suppurative meningitis, the pellicle forms in a very short time. In tuberculous meningitis, it takes from twelve to twenty-four hours for the pellicle to form, although I have seen it form in as short a time as one hour. Some authors have described a pellicle formation in poliomyelitis and in lues of the central nervous system. I have observed a pellicle in poliomyelitis and in general paresis only very rarely. I have, however, observed a cer-

tain sediment in some cases of general paresis, tabes dorsalis and in certain cases of cerebrospinal lues. The sediment formed was flocculent in type, resembling the flocculi formed by the Noguchi test, or after the addition of sodium hydrate to the fluid of tuberculous meningitis.

The pellicle is formed by the separation of the heavier elements of the cerebrospinal fluid, so that microscopically one can see in the pellicle many leucocytes on a fibrinous background. (Fig. 33.)

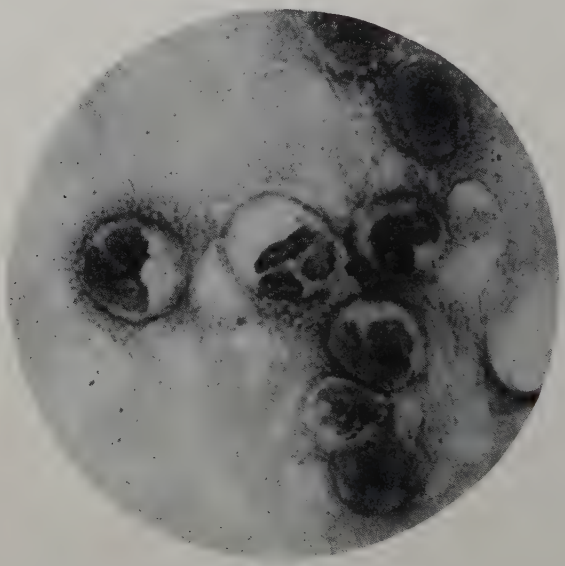

Fig. 33.—Photomicrograph of stained pellicle from cerebrospinal fluid of a pneumococcus meningitis.

Fig. 34 illustrates the various forms of pellicle in various diseases as observed early before autolysis takes place.

It has been generally agreed that the formation of a pellicle or "fibrin coagulum" is dependent upon the presence in the cerebrospinal fluid of fibrinogen and fibrin ferment. The addition of one drop of serum to meningitic fluid will supply the fibrin ferment and pellicle formation will then be hastened. The data on the fibrinogen content of the cerebrospinal fluid in relation to pellicle formation

are meager. The early workers on cerebrospinal fluid, such as Hoppe and Halliburton do not mention any determination of fibrinogen in their chemical examination. Coriat found no fibrinogen in fluid drawn postmortem from a case of hydrocephalus. Mestrezat also found no fibrinogen in normal fluid. Kirschenbaum and I found fibrinogen to be absent or present only in traces in normal cerebrospinal

A. *B.* *C.* *D.* *E.* *F.* *G.* *H.*

Fig. 34.—Pellicle formation in meningitis.

A. Normal. *B.* Meningococcus meningitis, fairly early. *C.* Meningococcus meningitis, advanced (sulphur-like granules). *D.* Meningococcus meningitis, late in disease. *E.* Meningococcus meningitis, severe, on road to recovery. *F.* Pneumococcus meningitis, fatal. *G.* Pneumococcus meningitis, fatal. *H.* Tuberculous meningitis.

fluid. In purulent meningitis we found an increase in the fibrinogen content of the cerebrospinal fluid. Even after the separation of a pellicle there remained an increased quantity of fibrinogen nitrogen. Our finding of no fibrinogen in the cerebrospinal fluid of 5 per cent of our cases

of tuberculous meningitis, although a pellicle formed in every one of these cases leads us to the inference that pellicle formation may be dependent on factors other than the presence of fibrinogen in the cerebrospinal fluid. At least, further study is necessary before it is possible to ascertain whether or not the pellicle is dependent on the presence of fibrinogen.

PHYSICOCHEMICAL CHANGES

Among the important changes that make their appearance in pathologic conditions of the nervous system are those of a physicochemical character. Although not all physicochemical changes are of diagnostic value, they are all of significance in that they bring out specific changes typical of special diseases. What is more, further investigations on the physicochemical changes taking place in pathologic cerebrospinal fluids give promise of an even wider range of information that can be applied with equal effectiveness to pathologic conditions of other body fluids, such as blood and urine.

Table XXXI will show some of the variations found in physicochemical constants in various pathologic conditions of the cerebrospinal fluid.

A comparison of these figures with those given for normal fluid (Chapter V) shows the great variation between the physicochemical constants of pathologic and normal fluids. Other authors have reported even greater differences. Achard, Loeper and Lanbry found the freezing point of fluid from tuberculous meningitis to be -0.44° C., and that of meningococcus meningitis -0.46° C., whereas the freezing point of normal fluid usually varies between -0.56° and -0.58° C.

In addition to the meningitides, the fluids of diabetes and uremia show changes in the freezing point. The fluid in diabetes has a freezing point of -0.62° to -0.69° C. The fluid in uremia has a freezing point of -0.63° to -0.73° C.

TABLE XXXI

PHYSICOCHEMICAL CONSTANTS IN VARIOUS FORMS OF MENINGITIS

	SPECIFIC GRAVITY	VISCOSITY	FREEZING POINT	CONDUCTIVITY	H-ION CONCENTRATION	ALKALI RESERVE	REFRACTOMETRIC INDEX
Suppurative meningitis	1.0075	1.07 1.14	–.55° to –.57° C.	.011629	Immed. P_H 7.3 On Standing P_H Increases slowly or may become more acid	18–38% of CO_2	1.33487 1.33644
Tuberculous meningitis	1.00693– 1.00626	1.05 1.18	–.47°	.013660	7.4– 7.6 Increases to 8.1 and higher	33–58% of CO_2	1.33475 1.33616

Serby and I found that in active and inactive syphilis of the central nervous system, the refractometric index varied between 1.33513–1.33557, with an average of 1.33525. We found that a marked increase in the viscosimetric and refractometric indexes of the cerebrospinal fluid is indicative of a pathologic process in the cerebrospinal fluid. For practical purposes, however, such determinations are unnecessary.

Spectrum Analysis

In bloody fluids, the usual spectroscopic absorption bands of blood may be seen. Urobilin in cerebrospinal fluid gives a typical broad absorption band between the Frauenhöfers lines E and F in green. Otherwise no typical changes occur in pathologic processes.

Crystallization

Another physical phenomenon which takes place in cerebrospinal fluid on standing, is the formation of crystals, their character depending on the character of the disease.

Various authors have called attention to the crystals found in the cerebrospinal fluid. Mott speaks of cholin crystals in the fluid of patients suffering from diseases producing a

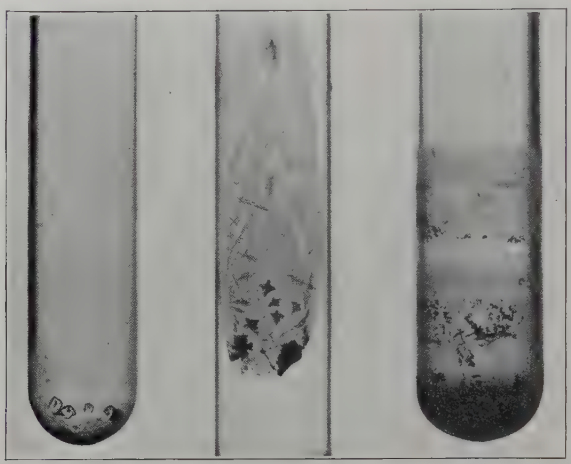

Fig. 35.—Crystals in test tube on spontaneous evaporation of cerebrospinal fluid from a case of tuberculous meningitis.

Fig. 36.—Spontaneously evaporated fluid from another case of tuberculous meningitis.

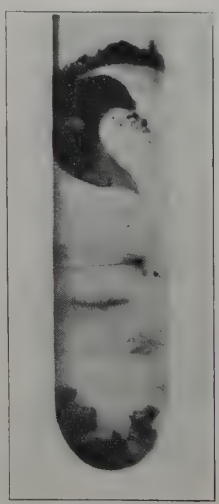

Fig. 37.—Spontaneously evaporated cerebrospinal fluid from a case of pneumococcus meningitis.

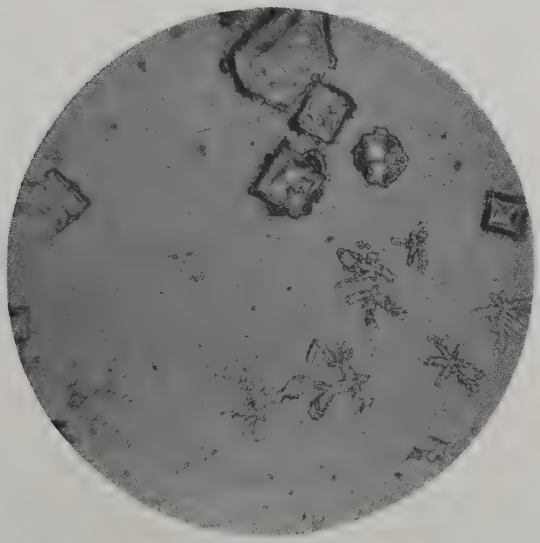

Fig. 38.—Crystals from an evaporated fluid in a case of tuberculous meningitis. (76 diameters.)

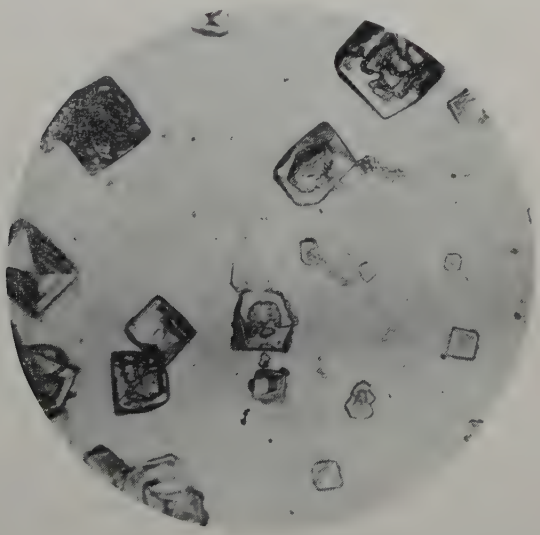

Fig. 39.—Crystals from another evaporated fluid of a case of tuberculous meningitis. (76 diameters.)

degeneration of the nervous tissue. Thomson describes the presence of elongated, colorless, transparent crystals in septic meningitis. He suggests that the acid radical present in the crystals is most likely phosphoric acid. I made a study of the crystalization process in a great number of pathologic fluids which were allowed to evaporate spontaneously at room temperature, and found that after several months of standing, most pathologic fluids showed the presence of many crystals of various sizes and shapes

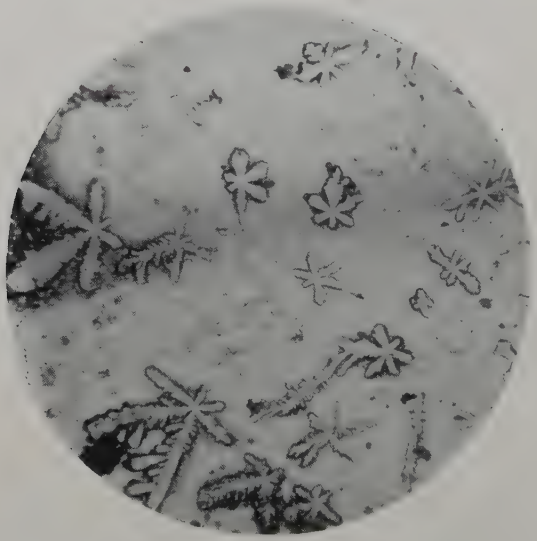

Fig. 40.—Crystals from an evaporated fluid of a case of pneumococcus meningitis. (76 diameters.)

different from those formed in normal fluids. Figs. 35, 36 and 37 show the different forms of crystals present in different conditions, the varieties being even more distinct on microscopic examination. (Figs. 38, 39 and 40.)

Turbidity

By using one c.c. of cerebrospinal fluid in a test tube one-third inch in diameter, and adding small portions of decinormal sodium hydrate or decinormal sulphuric acid to

the fluid, I was able not only to detect the presence of a pathologic process, but also to get a clue as to the type of the disease. Normal cerebrospinal fluid shows no turbidity on the addition of either sulphuric acid or of sodium hydrate. The fluid of tuberculous meningitis is not affected by sulphuric acid, but is precipitated by a very small amount of sodium hydrate. The fluid of suppurative meningitis, which is turbid to begin with, is cleared up by sodium hydrate and is not affected by sulphuric acid.

Protein Charges

It is well known that the electrical charge of a protein depends on the reaction of the medium. In acid solution, proteins become electropositive, and in alkaline solutions they become electronegative, as shown in Table XXXII taken from Michaelis.

TABLE XXXII

SHOWING CATAPHORESIS OF PROTEINS

SUBSTANCES	H^+	MOVES TO
Casein	4.9×10^{-5}	Cathode
	4.1×10^{-5}	Stand still
	1.3×10^{-5}	Anode
Serum Albumin	1.2×10^{-4} — 2.1×10^{-5}	Cathode
	2.0×10^{-5} — 1.9×10^{-5}	Stand still
	1.1×10^{-5} — 1.9×10^{-5}	Anode
Oxyhemoglobin	2.4×10^{-7}	Cathode
	1.2×10^{-7}	Anode
Gelatin	1.5×10^{-5}	Anode
	1.2×10^{-5} — 3.5×10^{-5}	Stand still
	3.9×10^{-5}	Cathode

It is thus seen that one way of precipitating protein is to let it combine with some radicle to form an insoluble protein salt. From the standpoint of the electrical charge

of the protein such a protein is necessarily either a positive protein radicle forming a protein salt with negatively charged ions (alkaloidal precipitants), such as tungstic, picric, tannic acid and the like, or a negatively charged protein combining with a positively charged metal (metallic precipitants) such as Cu, Ag, Hg, Zn, and Pb. If these protein salts are sufficiently insoluble, a precipitate will come down.

To ascertain whether the difference in the acidity of the cerebrospinal fluid under various conditions as discussed

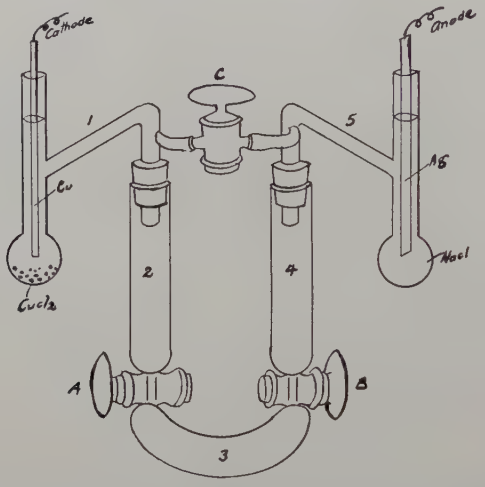

Fig. 41.—Apparatus for cataphoresis of proteins, after Michaelis.

below is great enough to produce different electrical states of the proteins in the fluids, Tashiro and I have made a series of observations. The apparatus used was the one recommended by Michaelis. (Fig. 41.)

The fluids were placed in 3, care being taken to see that there was no bubble inside the core of the stopcocks. Tubes 2 and 4 were filled with 3 per cent sulphosalicylic acid, and the upper portions (1 and 5), with distilled water. To one electrode was added $CuCl_2$ and to the other NaCl; a silver electrode was put in the anode and a copper electrode

in the cathode. The poles were connected to a light circuit with 110 volt constant current, with an ordinary lamp in the circuit as resistance. The object was to determine the pole to which the protein would move. The migration of the protein from the cerebrospinal fluid was detected by the formation of a precipitate with sulphosalicylic acid in the arm. This method, of course, is necessarily crude. For an accurate test it would be necessary that the H-ion concentration, the osmotic pressure of the precipitants and of cerebrospinal fluid be the same for each experiment—a procedure almost impossible on account of the variation in the fluid. Furthermore, under these conditions, positively charged protein has a better chance of forming precipitates at the cathode, while negatively charged protein, which moves to the anode, must change its charge at the anode in order to combine with sulphosalicylic acid. In other words, the amount of negatively charged protein to be precipitated at the anode depends not only on the amount of

TABLE XXXIII

RESULTS OF CATAPHORESIS ON FLUID FROM CASES OF TUBERCULOUS MENINGITIS

NO.	TIME AFTER WITHDRAWAL	CATAPHORESIS	
		Cathode	Anode
1	2 hours	↓	⇓
1	2 days	⇓	⇓
1	2 days	↓	⇓
2	2 hours	↓	⇓
2	3 hours	↓	⇓
3	1 day	↓	⇓
4	3 hours	↓	⇓
5	24 hours	↓	⇓

⇓ Indicates heavy precipitate.
↓ Slight precipitate.

protein that moves to the anode, but also on the strength of the acidity of the precipitating agent at the anode. Although this method is quite crude it is convenient for detecting the charge of protein in the cerebrospinal fluid.

Tables XXXIII and XXXIV show some of the results obtained on cerebrospinal fluid with the cataphoresis experiment.

As is seen from the tables, a considerable amount of the protein in meningococcus meningitis moves toward the cathode, showing the presence of positively charged pro-

TABLE XXXIV

RESULTS OF CATAPHORESIS ON FLUIDS FROM MENINGOCOCCUS MENINGITIS

NO.	INTERVAL	CATAPHORESIS		REMARKS
		Cathode	Anode	
1	1 day	↓	↓	
1	1 day	↓	↓	
2	20 hours	↓	↓	
2	3 days	↓	↓	
3	3 days	↓	↓	
3	2 days	↓	↓	Fluid bloody
3	3 hours	↓	↓	
4	8 hours	↓	↓	Unusually alkaline fluid; cases not under author's care; administration of serum not ascertained.
5	3 hours	↓	↓	
6	.....	↓	↓	
6	17 hours	↓	↓	
7	.....	↓	↓	
7	2 days	↓	↓	

↓ Indicates heavy precipitate.

↓ Slight precipitate.

tein in the cerebrospinal fluid of that disease. In tuberculous meningitis, however, the precipitate moves toward the anode, showing that the protein in that case is negatively charged. This again indicates the occurrence of specific biochemical changes in various diseases.

The Colloidal Gold Reaction

The work of Zsigmondy who found definite measures of the protective action of colloids on the precipitation of gold suspensions by sodium chloride, has been applied by Lange, to the protein of cerebrospinal fluid. Lange found that normal cerebrospinal fluid when diluted with 0.4 per cent solution of sodium chloride does not affect the solution of colloidal gold, while pathologic fluid produces characteristic changes for various diseases. The exact mechanism of the gold chloride reaction is not well known, but we have here a distinct physicochemical reaction that not only signifies the existence of a pathologic state of affairs, but also indicates its nature as this test produces specific discolorations in various forms of the same disease, such as in the various types of neurosyphilis.

The technic of the Lange test and of other tests mentioned in this chapter is given in Chapter XIII.

Mastic Reaction

Emanuel described a reaction obtained by adding a solution of mastic, the resin of Pistacia lentiscus, a tree of the Terebinthaceae to pathological cerebrospinal fluid. The mastic test seemingly works on the same principle as the Lange, and further corroborates the physicochemical specificity of disease.

Benzoin Reaction

In 1920, Guillain and Lechelle described a colloidal benzoin test using 16 tubes, which also showed specific changes in various conditions.

Other Colloidal Tests

Many other colloidal reactions have been described. All of these methods are more or less specific in various conditions, but are either too difficult to perform or not reliable enough for general use. Among the most important of these are the Berlin blue reaction of Kirschberg, the gamboge reaction of Riddel and Stewart, the collargol reaction of Stern and Poengsen, the colloidal paraffin reaction of Kafka, and the recent Targowla reaction.

Ninhydrin Reaction

Noble has applied the ninhydrin reaction of Abderhalden to the cerebrospinal fluid and found that in tuberculous meningitis a blue to a blue-violet color appears on boiling 0.5 to 1 c.c. of cerebrospinal fluid with 0.1 c.c. of 1 per cent ninhydrin solution for about one-half of a minute. Other workers have confirmed his observations.

Changes in the Reaction of the Cerebrospinal Fluid

Kopetzky applied the acidosis theory of Fischer to cerebrospinal fluid, claiming that the fluid presents an acidity of varying degree in all conditions which give rise to pressure symptoms of the brain. Kopetzky used litmus paper for his determination of the reaction and he also titrated the cerebrospinal fluid against decinormal sodium hydroxide solution. He expressed his results in grains of decinormal hydrochloric acid solution, estimated for 100 c.c. of cerebrospinal fluid, using a one per cent phenolphthalein solution as an indicator.

I studied the reaction of cerebrospinal fluid in disease from various points of view using the titration, the H-ion concentration and the alkali reserve methods for this purpose. Originally I determined the reaction of the cerebrospinal fluid by titrating the fluid against n/100 sulphuric acid. The following method was used:

In each of three Erlenmeyer flasks with a capacity of 50 c.c., 20 c.c. of distilled water was measured, all of the flasks being of the same height and width. Into each flask was put 1 drop of a 0.2 per cent solution of methyl red. This produced a straw-red color which was the neutral point. Then 1 c.c. of the fluid to be examined was placed in one of the flasks by means of a graduated pipette. This turned the solution still deeper yellow. The flask was now titrated with n/100 sulphuric acid until the neutral point was obtained. This was compared with the other two flasks, all three flasks being placed on a porcelain stand. When the neutral point was reached the reading was taken and then one more drop of the sulphuric acid was introduced. A bright red color appeared. In order to check the result 1 drop of n/100 NaOH was added. This gave the solution a straw color. Another drop was added which changed it to yellow, thus proving that the end point had not been overrun. This procedure gave no difficulty in obtaining a sharp end point.

With this method it was found that nonmeningitic fluid required between 1.5 and 2.6 c.c. n/100 sulphuric acid to reach the end point which would correspond to an alkali reserve varying between 33 and 58 per cent total CO_2. Fluid from meningococcus meningitis required between 0.7 and 1.3 c.c. of n/100 sulphuric acid which would correspond to an alkali reserve varying between 18 and 29 per cent total CO_2 and fluid from pneumococcus meningitis, the same amount. Tuberculous meningitis, however, acted the same as nonmeningitic fluid, requiring 1.5 to 2.6 c.c. of n/100 sulphuric acid to reach the end point. (Table XXXV.)

After I had completed my investigation of the reaction of the cerebrospinal fluid by means of this titration method, it was realized that the fluid on which the work had been done had been standing too long before examination to give an accurate idea of the real acidity of the fluid. I was also aware of the fact that the titrable acidity does not rep-

TABLE XXXV

TITRATION OF CEREBROSPINAL FLUID WITH METHYL RED AS INDICATOR

CASE	AGE	DIAGNOSIS	ALKALINITY IN TERMS OF N/100 H_2SO_4 WITH METHYL RED AS INDICATOR	OTHER TESTS	REMARKS
			A—NONMENINGITIC		
1	11 yrs.	Epilepsy	2.2 c.c.	Negative	
2	12 yrs.	Typhoid	2.2	Negative	
3	8 yrs.	Encephalitis	2.4	Negative	
4	40 yrs	Lues	2.2	Wassermann Positive	
5	Adult	Cerebrospinal Lues	1.8	Wassermann Positive	
6	Adult	Insanity	1.9	Negative	
7	Adult	Insanity	2.0	Negative	
8	Adult	Nephritis	2.2	Negative	
9	11 mos.	Otitis media, pneumonia	1.5	Negative	
10	5½ mos.	Erysipelas	1.9	Negative	
			B—MENINGITIC		
11	11 yrs.	Meningococcus meningitis Before serum	0.9 c.c.	Increased pressure. 41,200 cells, 100% polymorphonuclear. Meningococci in smear and culture.	After 3 doses of serum acidity 2.0 c.c.
12	10 yrs.	Meningococcus meningitis Before serum	0.9 c.c.	2,400 cells, 99% polymorphonuclear. Meningococci in smear and culture.	
13	4 yrs.	Meningococcus meningitis Before serum	0.7 c.c.	Several thousand cells per c.mm. 95% lymphocytes. Meningococci in direct smear and culture.	After serum 1.5 c.c.
14		Pneumococcus meningitis	0.9 c.c.	Chemical tests positive. Pneumococci in culture.	
15		Pneumococcus meningitis	1.1 c.c.	Pneumococci in culture.	
16	3 yrs	Tuberculous meningitis	1.9 c.c.	Tubercle bacilli found in fluid.	
17	20 mos.	Tuberculous meningitis	2 c.c. 2.1 c.c.	All chemical tests positive.	Autopsy proved diagnosis.

resent the true hydrogen-ion concentration of the fluid although it does tell the titrable acidity or alkali reserve. I, therefore, decided to determine whether there was a similar variation in the free hydrogen-ion concentration between the normal and meningitic fluids of special types. To make the test the gas-chain method of Michaelis was used, and, benefiting by the experience with nonmeningitic fluid, I

TABLE XXXVI

H^+ CONCENTRATION OF FLUID FROM TUBERCULOUS MENINGITIS

No.	PH										
	Immediate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1									8.69(a)	8.98(a)	
2										7.9 (a)*	
3				7.9 (b)							
4				8.0 (b)						8.0 +(b)	8.6 (b)
5											8.6 (b)
6	7.4 (b)										
7	7.4 (b)										
8	7.4 (b)										
9	7.4 (b)										
10	7.4 (b)							8.0 (b)		8.0 +(b)	
11				7.6 (c)			8.2 (c)				
12	7.4 (b)										
13										8.2 (c)	
14	7.4 (c)									8.2 (c)	
15											8.0(c)*
16											8.1 (c)
17								8.0 (c)			
18			8.1 (c)						8.8 (a)		
19	7.4 (c)					8.1 (c)					
20										7.8 (c)*	
21	7.4 (c)				7.8 (c)		7.9 (c)				
22									8.1 (c)		
23									8.1 (c)		
									8.4 (a)		
24								7.7 (c)			
25	7.6 (c)										
26	7.4 (c)	7.6 (c)	7.6 (c)	7.8 (c)	7.8 (c)					8.1 (c)	
										8.5 (a)	
27				7.75(a)							
				7.7 (c)							
28	7.4 (c)		7.6 (c)							8.2 (c)	

*Corked.

endeavored to examine fluid as soon after removal from the body as possible. To carry out the immediate examination it was often necessary to resort to the indicator method, using the Levy-Rowntree-Marriott standard and a special indicator, checking both indicators by the gas-chain apparatus. In over a hundred cases of meningitis examined and checked by the above methods, the following observations were made:

Fluid from cases of tuberculous meningitis differed in no respect from that of normal cases, the P_H being 7.4-7.6 immediately after withdrawal and ascending to 8.1 or higher. In some tuberculous fluids the H-ion concentration decreased in a much shorter time than in normal fluid (Table XXXVI).

Fluid from cases of meningococcus meningitis showed an H-ion concentration slightly higher than that of normal, the P_H being 7.2 to 7.5 immediately after withdrawal, the average being 7.3. The greatest deviation from normal, however,

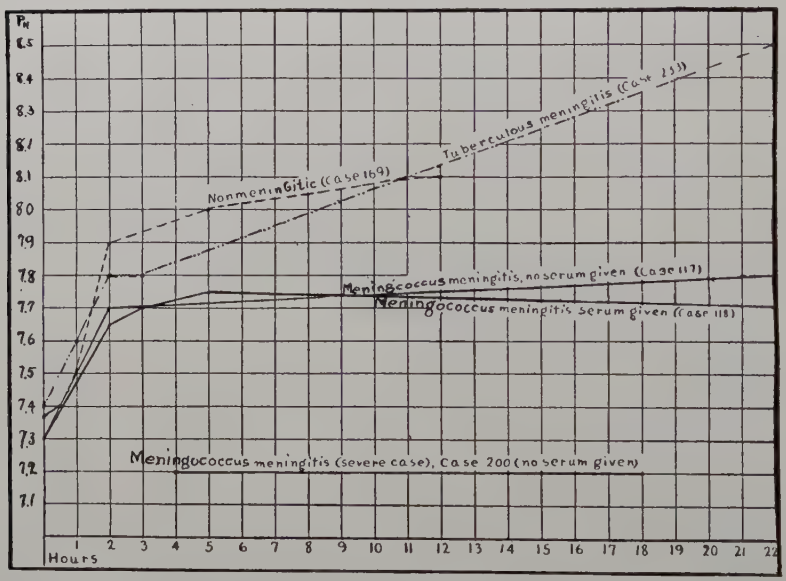

Fig. 42.—Change in the H+ concentration of three types of cerebrospinal fluid.

was observed in fluid allowed to stand, the H-ion concentration then decreasing slowly in some cases, remaining stationary in others, and increasing in still others. Usually the graver the condition of the patient, the more turbid the fluid, and the longer the retention of the acidity. Administration of serum altered the H-ion concentration of the fluid, generally decreasing it. Cases of pneumococcus meningitis showed a strong resemblance to those of

Table XXXVII

H+ Concentration of Fluid of Meningococcus Meningitis Before Administration of Serum

No.	PH										
	Immediate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days orOver
1	.....	.....	.....	.....	.....	.....	.....	.....	7.4 (b)		
2	7.4 (b)										
3	.....	.....	.....	.....	.....	.....	7.0 (b)				
4	7.1 (c)	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.8 (c)
5	7.3 (c)	.....	.....	7.7 (c)	.....	.....	.....	.....	.....	7.8 (c)	
6	.....	.....	.....	.....	.....	.....	.....	7.4 (c)			
7	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.2 (c)
8	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.1 (c)
9	.....	.....	.....	.....	.....	.....	.....	.....	7.9 (c)		
10	.....	.....	.....	.....	.....	.....	.....	.....	7.9 (c)		
11	.....	.....	.....	.....	.....	.....	.....	7.4 (c)			
12	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.8 (c)	
13	.....	.....	.....	.....	.....	7.2 (c)	.....	.....	7.2 (c)	.....	7.1 (a)
14	.....	.....	.....	.....	.....	7.3 (c)					
15	.....	.....	.....	.....	.....	7.3 (c)	.....	.....	.....	7.4 (c)	7.2 (c)
16	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.7 (c)	7.8 (c)
17	.....	.....	.....	.....	7.7 (c)						
					7.7 (a)						
18	7.3 (c)	7.4 (c)	.....	.....	.....	.....	.....	.....	7.6 (c)	7.6 (c)	7.9 (c)
19	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	6.6 (c)
											6.0 (a)
20	7.4—(c)	.....	.....	.....	.....	.....	.....	.....	8.1 (c)		
	7.5										
21	7.3—(c)	.....	.....	.....	.....	.....	.....	.....	7.8 (c)		
	7.4								7.8 (a)	7.8 (a)	
22	7.3 (c)	.....	.....	.....	.....	.....	.....	.....	.....	7.9 (c)	

Table XXXVIII

H+ Concentration of Fluid of Meningococcus Meningitis After Administration of Serum

No.	PH										
	Immediate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days orOver
1	7.4—(b)										
2	7.4—(b)										
3	7.4—(b)										
4	.....	.....	.....	.....	.....	7.0 (b)					
5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.4 (b)
6	.....	.....	.....	.....	.....	.....	.....	.....	7.4 (b)		
7	.....	.....	.....	.....	.....	.....	.....	7.0 (b)			
8	.....	7 1 (b)	.....	.....	.....	.....	.....	.....	7.4 (b)		
9	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.1(c)	
10	.....	.....	.....	.....	.....	.....	7.4 (c)				
11	7.3 (c)										
12	.....	.....	.....	7.7 (c)							
13	.....	.....	.....	.....	.....	.....	.....	7.6 (c)	7.8 (c)		
14	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.2 (a)
15	7.1 (c)	.....	.....	.....	.....	.....	.....	.....	7.9 (c)		
16	.....	.....	.....	.....	.....	.....	.....	.....	8.1*		
17	7.3 (c)	.....	.....	7.6—7 (c)	.....	7.7—(c)	7.7—7.8 (c)	.....	.....	7.7 (c)	
18	.....	7.4	.....	.....	.....	.....	.....	.....	8.2		

* Diagnosis was not settled.

meningococcus meningitis. (Tables XXXVII and XXXVIII.) (Fig. 42.)

The slightly higher H-ion concentration of the fluid in suppurative meningitis as compared to normal, on immediate examination of the fluid, may be explained, I believe, by the bacterial fermentation of the dextrose in the fluid as indicated by the absence of sugar or the lessened amount of it in meningococcus meningitis—a fact

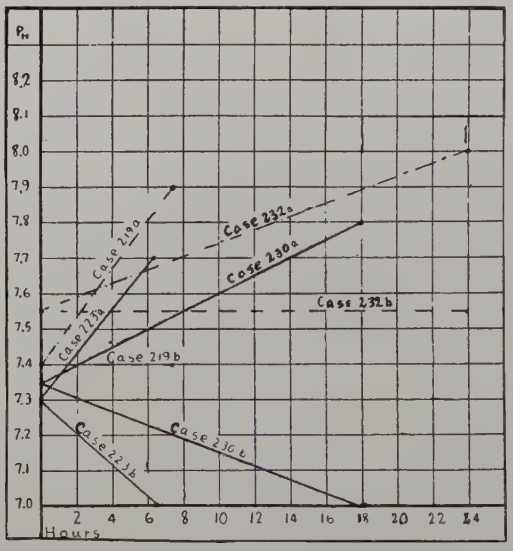

Fig. 43.—Different effects of corking on tuberculous and meningococcus fluids. Case 219a, tuberculous meningitis, cotton plugged; b, same fluid, tightly corked (no air above). Case 232a, tuberculous meningitis, cotton plugged; b, same fluid, corked (no air above). Case 223a, meningococcus meningitis, cotton plugged; b, same fluid, tightly corked (no air above); Case 230a, meningococcus meningitis, cotton plugged; b, same fluid, tightly corked (no air above).

that has been brought out by several investigators. As for the mechanism responsible for the slow decrease in the H-ion concentration of fluid from suppurative meningitis, there are several possibilities to be considered, such as a slower loss of CO_2 in the fluid upon standing, a constant CO_2 production by the cells present in the sediment of the

fluid, lactic acid formation due either to further fermentation of sugar by the bacteria in the test tube or to a destruction of the cells on standing of the fluid.

I found that the H-ion concentration of these fluids increased from 7.4 to 7.0 upon standing in tubes tightly corked, thus indicating that there is not only no loss of CO_2, but that there is also a formation of certain acids on standing. Nonmeningitic and tuberculous fluids give quite different results (Tables XXXIX and XL). (Fig. 43.)

With the view of further ascertaining the cause of this increase of acidity the following experiments were made:

In one chamber of the biometer (Tashiro) was put 1 c.c. of tuberculous meningitis fluid, and exactly the same amount of meningococcus fluid in the other chamber. It was found that the tuberculous fluid gave off more CO_2 than the meningococcus, showing that although both tuberculous and meningococcus fluids give off CO_2 constantly, tuberculous fluid loses more CO_2 than does meningococcus. This suggests that the increased acidity in meningococcus meningitis is not due to a greater production of CO_2 but probably to the production of some other acid, very likely lactic acid.

Further work on the subject showed a greater amount of lactic acid in the fluid of meningococcus and other forms of suppurative meningitides than in that of normal or of tuberculous meningitis. Furthermore, upon standing, the fluid of suppurative meningitides showed an increase in its lactic acid content. This was more marked in the fluids that contained many polymorphonuclear leucocytes. Many of our fluids that showed no acetone immediately after withdrawal, showed traces of it when allowed to stand for a day or two. These changes indicate that the increase, on standing, of the H-ion concentration of fluids from suppurative meningitides is due to a constant formation of organic acids, resulting from the decomposition of the cells in the fluid.

TABLE XXXIX

TUBERCULOUS FLUID, CORKED

DATE DRAWN	DATE EXAMINED	INTERVAL	HOW STOPPERED	PH
6/28/17 9:10				7.4
	6/28/17 3:05	5 hours	Cork	7.4
	6/28/17 3:05	5 hours	Cotton	7.9
7/13/17 11 a. m.	7/13/17 11 a. m.	Immediately		7.5–6
7/13/17	7/14/17 11 a. m.	24 hours	Cork	7.5–6
7/13/17	7/14/17 11 a. m	24 hours	Cotton	8.0

TABLE XL

FLUID FROM MENINGOCOCCUS MENINGITIS, WITH CORK AND COTTON STOPPER

DATE DRAWN	DATE EXAMINED	INTERVAL	STOPPERED WITH	PH
6/30/17 12:20 p.m.	6/30/17 12:20 p.m.	Immediate		7.3
	6:35 p.m.	6¼ hours	Paraffined cork	7.0
	6:35 p.m.	6¼ hours	Cotton plug	7.7
7/6/17 2:30 p.m.	7/6/17 2:30 p.m.	Immediate		7.4
	7/7/17 8:30 a.m.	18 hours	Paraffined cork	7.3
	7/7/17 8:30 a.m.	18 hours	Cotton	8.2
7/11/17 11:30 a.m.	7/11/17	Immediate		7.4–7.5
	7/12/17 4:30 p.m.	17 hours	Paraffined cork	7.4
	4:30 p.m	17 hours	Cotton	8.1
7/11/17 1:30 p.m.	7/11/17 1:30 p.m.	Immediate		7.3–7.4
	7/12/17 7:30 a.m.	18 hours	Paraffined cork	7.0
		18 hours	Cotton	7.8
7/14/17	7/14/17	Immediate		7.3
	7/15/17	22 hours	Paraffined cork	7.1
		22 hours	Cotton	7.9

Precipitation

The action of precipitants on cerebrospinal fluid in various diseases furnishes further evidence of the varying character of the protein in different diseases. Tashiro and I found that in certain pathologic conditions a characteristic ratio may be obtained between the precipitate formed

1. *2.* *3.* *4.* *5.* *6.*

Fig. 44.—Photograph showing the typical ratio of precipitates by the two precipitants.

1. 1 c.c. of nonmeningitic fluid plus 1 c.c. of 3 per cent sulphosalicylic acid.

2. 1 c.c. of nonmeningitic fluid plus 1 c.c. of 1 per cent $HgCl_2$.

3. 1 c.c. of fluid from tuberculous meningitis plus 1 c.c. of sulphosalicylic acid.

4. 1 c.c. of fluid from tuberculous meningitis plus 1 c.c. of $HgCl_2$.

5. 1 c.c. of fluid from meningococcus meningitis plus 1 c.c. of sulphosalicylic acid.

6. 1 c.c. of fluid from meningococcus meningitis plus 1 c.c. of $HgCl_2$.

by sulphosalicylic acid and that formed by mercuric chloride. We based our comparison on the assumption that different processes respond differently to alkaloidal precipitants, such as sulphosalicylic acid and metallic precipitants, such as mercuric chloride (Tables XLI, XLII, and XLIII, Fig. 44).

These findings speak in favor of my contention that there are specific changes produced by various disease processes which manifest themselves both chemically and physicochemically. Although the fluid in cases of tuberculous meningitis contains less organic substances than the fluid of meningococcus meningitis as the table on organic index shows, still the mercuric chloride solution produces a heavier sediment in tuberculous meningitis than it does in meningococcus meningitis. Table XLIV shows further that the precipitants in question do not bear any quantitative relation to the amount of protein present in the cerebrospinal fluid.

TABLE XLI

COMPARISON OF AMOUNT OF SEDIMENT FROM THE METALLIC AND ALKALOIDAL PRECIPITATION WITH NONMENINGITIC FLUIDS

NUMBER	DIAGNOSIS	MEASUREMENTS OF THE DEPTH OF SEDIMENT IN MM. AFTER 24 HOURS	
		$HgCl_2$	Sulphosalicylic Acid
1	Psychosis	3	2
2	Tic	4	3
3	General paresis	4½	2
4	Delirium tremens	3	1
5	General paresis	3½	2
6	Psychosis	3	2
7	General paresis	3½	2
8	General paresis	3	0
9	Psychosis	4	3
10	Psychosis	4	0
11	Psychosis	4	2
12	Meningism	3	2
13	Dementia precox	3	0
14	Alcoholic	3	2
15	Psychosis	3	2
16	Psychosis	4	2
17	Psychosis	3	1
18	Psychosis	2½	2
19	Meningism	3	2

TABLE XLII

AMOUNT OF SEDIMENT FROM THE METALLIC AND ALKALOIDAL PRECIPITATION FROM FLUID OF TUBERCULOUS MENINGITIS

	MEASUREMENTS OF THE DEPTH OF SEDIMENT IN MM. AFTER 24 HOURS	
NUMBER	$HgCl_2$	Sulphosalicylic Acid
1	10	4
2	15	4
3	10	3½
4	11	5
5	6	3
6	7	3
7	9	6
8	13	5
9	11	7
10	10	4
11	6	3
12	10	4
13	20	5

TABLE XLIII

MEASUREMENT OF SEDIMENT FROM METALLIC AND ALKALOIDAL PRECIPITATION FROM FLUID IN MENINGOCOCCUS MENINGITIS BEFORE SERUM WAS GIVEN

	MEASUREMENTS OF THE DEPTH OF SEDIMENT IN MM. AFTER 24 HOURS	
NUMBER	$HgCl_2$	Sulphosalicylic Acid
1	1	8
2	2	7
3	1	20
4	1	10
5	7	20

Originally, a 3 per cent sulphosalicylic acid and a 1 per cent mercuric chloride solution was used. Pons and Fletcher modified the test, using a 6 per cent sulphosalicylic acid and a 2 per cent mercuric chloride solution, corroborating the finding of a positive test in 95 per cent of their cases of tuberculous meningitis. Giordano and Abelson found the test to give false reactions in 17 per cent of their cases of tuberculous meningitis. Peterman used 4 per cent sulphosalicylic acid and a 2 per cent mercuric chloride and confirmed the result in 34 cases of meningococcus and 17 of tuberculous meningitis studied by him. He

believes that "next to finding the bacilli, the sulphosalicylic acid-mercuric chloride test is the most valuable diagnostic aid in tuberculous meningitis." Perlstein using a 3 per cent sulphosalicylic acid and a 2 per cent mercuric chloride solution found the ratio of the mercuric chloride to sulphosalicylic acid precipitate to be above 2 in 16 out of 17 cases, and above 3 in 8 out of 17 cases of tuberculous meningitis. Ratios above 3, according to him are practically pathognomonic for tuberculous meningitis.

TABLE XLIV

CASE	DIAGNOSIS	APPEARANCE OF FLUID	AMOUNT OF PROTEIN	MERCURIC CHLORIDE SEDIMENT After 24 hours	SULPHOSALICYLIC ACID SEDIMENT After 24 hours
230	Tuberculous meningitis	Clear	0.1%	20 mm.	5 mm.
231	Tuberculous meningitis	Clear	0.1%	18 mm.	7 mm.
232	Tuberculous meningitis	Clear	0.9%	14 mm	6 mm.
233	Meningococcus meningitis	Turbid	0.3%	5 mm.	20 mm.
234	Meningococcus meningitis	Turbid	0.25%	7 mm.	20 mm.

Permeability of the Meninges

Under normal conditions there is an effective "hematocephalic barrier," presumably in the meninges, which prevents substances in the blood from passing over into the cerebrospinal fluid. Under pathologic conditions this barrier is damaged and an increased permeability of the meninges occurs. Cohen has attempted to explain all the changes that occur in the cerebrospinal fluid in meningitis on the basis of changes in meningeal permeability. These changes are so constant and characteristic that he has formulated what he calls the "meningitis law." According to this law, the changes occurring in the cerebrospinal fluid in meningitis may be classed under four headings:

1. An increased concentration in the cerebrospinal fluid

of those substances present normally in greater quantity in the blood; for example, protein, inorganic phosphorus, cholesterol. The exception to this rule is glucose the concentration of which in the cerebrospinal fluid is decreased in meningitis. This is probably due to the utilization of the glucose by the organisms and cells present in the cerebrospinal fluid.

2. A decrease in the cerebrospinal fluid of those substances normally present in greater quantities in the cerebrospinal fluid than in the blood; i.e., chlorides and (according to Cohen) magnesium. Normally the blood contains 570–640 mg. and the cerebrospinal fluid 700–760 mg. of chlorides. In meningitis, the cerebrospinal fluid chlorides are decreased, but never to a point below that of the blood chlorides.

3. The presence in the cerebrospinal fluid of substances normally absent from the cerebrospinal fluid but present in the blood; e.g., fibrinogen, which causes a pellicle.

4. Passage into the cerebrospinal fluid of substances injected into the blood which normally do not pass the chorioid plexus; e.g., potassium iodide, nitrates, salicylates, uranin (sodium fluorescin), agglutinins, bile pigment, organic arsenic, etc.

These changes, according to Cohen, indicate that the permeability of the chorioid plexus or of the meningeal vessels is responsible for them.

Bromide Test of Walter

Walter showed that under normal circumstances a patient who had been given bromides had a definite ratio between the bromide content of the cerebrospinal fluid and that of the blood, and that in pathologic conditions, this ratio varied. Malamud, Fuchs and Malamud showed that normally the Permeability Quotient

P. Q. = Bromide content of blood ÷ bromide content of cerebrospinal fluid

is 3; in general paresis, cerebrospinal lues and arteriosclerotic dementia, this quotient is lowered; that is, the permeability is increased, and in dementia precox the quotient is increased; that is, permeability is decreased.

Biologic Tests

Many tests for biologic substances in the cerebrospinal fluid have been advanced as tests for meningeal permeability. Eil and Kafka use the hemolysin test (described on page 285) as a means of estimating permeability of the meninges. Dujardin has used the quantitative estimation of the amount of "reagin" in the cerebrospinal fluid of syphilis as an index of meningeal permeability.

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CHAPTER X

PATHOLOGIC CEREBROSPINAL FLUID CHEMICAL AND BIOCHEMICAL CHANGES

CHEMICAL CHANGES

In all organic disturbances of the meninges, there are chemical changes of various degrees. These changes are due most likely to changes in the permeability of the meninges.

INORGANIC CONSTITUENTS

Chlorides

In nephritis, with retention of chlorides, the chloride content of the cerebrospinal fluid is increased. In meningitis, the chlorides are decreased, the decrease being greatest in tuberculous meningitis. Freemont-Smith and Ayer found the chlorides to be reduced to 640-720 mg. in purulent meningitis and even below 640 in tuberculous meningitis. Steiner and Beck give the normal chloride content of cerebrospinal fluid as 680 to 720 mg. per 100 c.c. In tuberculous meningitis they found the chloride content to be as low as 560 to 680 mg.; in meningismus, 620-680 mg., and in a case of eclampsia and in one of encephalitis they found an increase to 760-800 mg. It may be safely said that a cerebrospinal fluid chloride content below 600 mg. per 100 c.c. speaks for the presence of tuberculous meningitis. Under no condition does the chloride content of the cerebrospinal fluid fall below that of the blood. In certain acute infections, notably pneumonia, there may be a moderate decrease in chlorides. The same holds true of Froin's syndrome. In all other conditions, e.g., brain abscess or tumor, the chloride content of the cerebrospinal fluid is normal.

Calcium

The calcium content of the cerebrospinal fluid has been the subject of much recent investigation, especially in its relation to headache and to tetany.

Depisch and Richter-Quittner, observed a diminution in the calcium content of the cerebrospinal fluid in pathologic conditions associated with headache. These observations, however, were not confirmed by the work of Critchley and O'Flynn. The latter workers found that in tetany the cerebrospinal fluid calcium is decreased, but it is not decreased as much as the blood calcium. In the convalescent stage of tetany, the calcium content of the cerebrospinal fluid returns to normal more rapidly than does the blood calcium.

Neustaedter, Hala and Tolstoouchow observed a decrease in the calcium content of the cerebrospinal fluid in cases of chorea, and an increase in cases of brain abscess and tumor. In spinal compression with a Froin syndrome, the calcium content of the cerebrospinal fluid is increased according to Critchley and O'Flynn.

The calcium content of the cerebrospinal fluid in meningitis has been investigated by Critchley and O'Flynn, in epilepsy by Osnato, Killian, Garcia and Mattice and in manic-depressive insanity by Weston and Howard. In all of these conditions, the normal calcium content of the cerebrospinal fluid was found.

Magnesium

Cohen observed that normally cerebrospinal fluid magnesium content exceeded the blood magnesium content by 20 to 30 per cent, but that in meningitis this excess became diminished, similar to the diminution of chlorides in meningitis.

Sodium and Potassium

There are no appreciable changes in the sodium and potassium content of the cerebrospinal fluid in pathologic conditions. In meningitis, they approximate their concentrations in the blood a little more closely.

Inorganic Phosphorus

In meningitis, purulent, tuberculous and luetic, the inorganic phosphorus content of the cerebrospinal fluid is increased. In lethargic encephalitis, on the other hand, there is no such increase, a point of diagnostic importance. In chronic affections of the central nervous system there is a slight increase in the inorganic phosphorus content of the cerebrospinal fluid. Cohen believes that the increase in the phosphorus content of the cerebrospinal fluid in pathologic conditions is not due to a breaking down of nerve tissue, but rather to an increased permeability of the meninges, so that the concentration of phosphates in the cerebrospinal fluid never exceeds that of the blood. Donath found the phosphates in the cerebrospinal fluid to be increased in general paralysis, tabes dorsalis and brain tumor. There is no relation between phosphate content and Wassermann reaction. In Froin's syndrome, there is an increased phosphorus content of the cerebrospinal fluid probably due to seepage of blood into the cerebrospinal fluid.

Lead

The meninges are normally impermeable to lead. Weller and Christensen have demonstrated lead in the cerebrospinal fluid of animals dying in convulsions following the administration of lead. In all of these cases, however, the meninges were shown to be damaged.

In lead meningo-encephalitis, lead may be present in the cerebrospinal fluid. Fairhall has described a hexanitrite test for the estimation of lead in cerebrospinal fluid.

Arsenic

Brahme has shown that under normal conditions arsenic given by mouth or intravenously permeates the meninges not at all or only in traces. Under pathologic conditions, such as syphilis of the central nervous system large quan-

tities of arsenic were found by him in the cerebrospinal fluid. This observation has been confirmed by many workers.

ORGANIC CONSTITUENTS

Permanganate, Reduction or Organic Index

Mayerhofer was able to show by means of the Kubl Thiemich permanganate method that there is an increase in the organic substance in cerebrospinal fluid in all meningitides. This increase, he found, could be measured by the amount of permanganate necessary to oxidize the organic substance. Mayerhofer's observations led him to the following conclusions:

(1) That the reduction index of normal cerebrospinal fluid is below 2. Different portions of the same fluid give either the same reduction index or a different one, the tendency being toward a higher index in each subsequent portion.

(2) That the reduction index of cerebrospinal fluid in meningitis is higher than that of normal cerebrospinal fluid (2 and up). Unlike normal fluid, the index becomes lower with each subsequent portion of the fluid.

(3) That the reduction index of cerebrospinal fluid in meningococcus meningitis drops to one-half its original pathologic rate after an injection of antimeningococcic serum.

My work on the permanganate index gave similar results. I found that fluid of all forms of meningitis gives a higher organic index than normal fluid and that the fluid of suppurative meningitides gives a higher organic index than fluid of tuberculous meningitis. Table XLV gives some of the findings with the permanganate index in fluid of various diseases.

Protein

In normal cerebrospinal fluid the protein content is small and consists mainly of globulin. In most pathologic con-

TABLE XLV

ORGANIC INDEX IN CEREBROSPINAL FLUID IN VARIOUS FORMS OF MENINGITIS

NO.	DIAGNOSIS	PERMANGANATE INDEX				
		TUBE I	TUBE II	TUBE III	TUBE IV	TUBE V
1	Tuberculous meningitis	3.0		3.0		
2	Tuberculous meningitis	2.9	2.6	3.2		
	(Same case, 4 days later.)	3.35			4.55 (15 c.c. between)	
3	Tuberculous meningitis	2.55	1.77	1.6		
	(Examined 2 days later)	2.95	1.55	1.75		
4	Tuberculous meningitis	3.1			2.7	2.7
	(Examined 3 days later)	3.9	1.8	3.0		
5	Tuberculous meningitis	2.1			1.8	
6	Tuberculous meningitis	2.6	2.2			
7	Meningococcus meningitis	7.9				
8	Meningococcus meningitis	5.6				
9	Meningococcus meningitis	2.0				
10	Meningococcus meningitis	9.2	9.3			
	(12 hours after serum injection)	7.3	8.7			
11	Influenza meningitis	2.6				
12	Pneumococcus meningitis	3.3	4.3	3.0		
	(Examined 7 days later)	4.6	4.3	4.6		
13	Pneumococcus meningitis	4.7		4.7	4.7	

ditions there is an increase in the amount of the protein, the increase usually varying with the severity of the disease. It has been found, however, that in some fatal cases of tuberculous meningitis, the fluid may contain a normal amount of protein. According to Mestrezat the albumin is mostly increased in acute inflammatory conditions, and the globulin is increased in syphilitic affections of the cerebrospinal system as Table XLVI of Mestrezat shows. (Figures expressed in grams per liter.)

TABLE XLVI

	SERUM ALBUMIN	GLOBULIN	RATIO OF SERUM ALBUMIN TO GLOBULIN
Tuberculous meningitis	1.15	0.15	7/1
	1.35	0.25	5.5/1
	0.80	0.40	2/1
Cerebrospinal meningitis	1.80	0.30	6/1
	2.50	0.31	8/1
Syndrome of massive coagulation	4.90	1.30	3/1
	6.50	2.20	3/1

Hektoen and Neymann studied the action of specific antiglobulin and antialbumin precipitins on cerebrospinal fluid. They found that in the fluid of general paresis both albumin and globulin are increased, but principally the globulin, while in the fluid of epilepsy the increase of protein seemed to be in the albumin. Kirschenbaum and I found albumin in 2 cases of epilepsy. We also found albumin in the fluid of tuberculous and suppurative meningitis, and in syphilis of the central nervous system.

Albumoses

Albumoses are absent from normal fluid. In Froin's syndrome, and in spinal compression by tumor or Pott's disease, they are frequently present. They have also been described in the fluid of tuberculous meningitis.

Urea, Uric Acid and Creatinine

The amount of these substances present in the cerebrospinal fluid runs parallel to the amount present in the blood. In uremia, all of these constituents are increased in the cerebrospinal fluid, the greatest increase being in the urea. Mestrezat states that all cases of nephritis with over 300 mg. of urea per 100 c.c. of cerebrospinal fluid are fatal. In chronic syphilitic conditions and in cases of cerebral arteriosclerosis the urea content may also be somewhat elevated.

In gout, according to Eskuchen, the uric acid content is elevated.

Sugar

The study of sugar in the cerebrospinal fluid in its relation to certain diseases of the meninges, has occupied an important place in the literature. Kopetzky found an entire absence of sugar in all cases of meningitis. His method of determination, however, was only qualitative. Connall reported an absence of sugar in all acute infections of the meninges. Schloss observed an absence of sugar in some cases of tuberculous meningitis and a small amount in others. Hopkins found a smaller amount of sugar in the fluid of syphilitics than in any other condition except meningitis. Steiner has also found a decrease to total absence of sugar in meningitis. He states that the sugar content of cerebrospinal fluid is increased in poliomyelitis, tetanus, and brain tumor. Alpers, Campbell and Prentiss found increased sugar in the cerebrospinal fluid in encephalitis lethargica and in dementia precox. Although the increase in these cases is not pathognomonic, it is of diagnostic importance.

Kasahara and Uetani working on rabbits found a decrease in cerebrospinal fluid sugar following subcutaneous injection of insulin, reaching its maximum two to three hours after injection and returning to normal in seven hours. Mestrezat and Depisch and Richter-Quittner observed a rise in cerebrospinal fluid sugar in chronic nephritis and in uremia. My work with Strouse on sugar in

Table XLVII

Sugar Content in the Cerebrospinal Fluid of Lues
(In Milligrams per 100 c.c.)

NO.	WASSERMANN TEST	SUGAR CONTENT
1	Strongly positive	104
2	Strongly positive	104
3	Positive	64
4	Strongly positive	48
5	Positive	70
6	Positive	74
7	Suspicious	80

TABLE XLVIII

SUGAR CONTENT IN CEREBROSPINAL FLUID OF DIABETES
(IN MILLIGRAMS PER 100 C.C.)

NO.	CEREBROSPINAL FLUID	SUGAR CONTENT	
		BLOOD	URINE
1	76	80	420
2	380		
3	280	240	

TABLE XLIX

SUGAR CONTENT IN THE CEREBROSPINAL FLUID OF MENINGITIS

NO.	DIAGNOSIS	SUGAR
1	Tuberculous meningitis	80
2	Tuberculous meningitis	Absent
3	Tuberculous meningitis	38
4	Tuberculous meningitis	32
5	Tuberculous meningitis	24
6	Tuberculous meningitis	Absent
7	Meningococcus meningitis	24
8	Meningococcus meningitis	28
9	Meningococcus meningitis	Absent
10	Meningococcus meningitis	Absent
11	Meningococcus meningitis	Absent
12	Pneumococcus meningitis	Absent
13	Pneumococcus meningitis	Absent

TABLE L

DIAGNOSIS	BLOOD SUGAR, MG. PER 100 C.C.	CEREBROSPINAL FLUID SUGAR, MG. PER 100 C.C.	PERCENTAGE RELATIONSHIP OF CEREBROSPINAL FLUID SUGAR TO BLOOD SUGAR
Tuberculous meningitis	120	14	12
	97	14	14
Tuberculous meningitis	112	22	20
	112	27	24
Tuberculous meningitis	112	28	25
Tuberculous meningitis	94	11	12
	116	12	10
Tuberculous meningitis	115	35	30
Tuberculous meningitis	145	34	23
Tuberculous meningitis	149	45	30
Tuberculous meningitis	94	19	20
Tuberculous meningitis	99	16	16
Tuberculous meningitis	102	29	28
Meningococcus meningitis	176	95	54*
	100	25	25†
Streptococcus meningitis	157	Trace	--
Influenza meningitis	84	26	31

*Twelve hours after onset, fluid turbid.
†After 150 c.c. serum.

pathologic cerebrospinal fluids showed no alteration of sugar in the fluid of lues and gave an increase of sugar in diabetes (Tables XLVII and XLVIII). My recent studies showed either an entire abscence or only small amounts of sugar in all forms of meningitis. The decrease is generally greater in purulent than in tuberculous meningitis (Table XLIX). I have also encountered normal values in the cerebrospinal fluid in cases of tuberculous meningitis. Occasionally early in the course of a tuberculous meningitis the sugar content may be increased.

In investigating the relation between the sugar content of the blood and cerebrospinal fluid in pathologic conditions, I found that in meningitis there was no change in the blood sugar (Table L). Table LI shows the effect of intravenous injection or ingestion of glucose upon cerebrospinal fluid and relation to blood sugar.

TABLE LI

EFFECT OF GLUCOSE ON SUGAR IN BLOOD AND CEREBROSPINAL FLUID

Name	Date	Diagnosis	Glucose	Blood Sugar Mg. per 100 c.c.	Cerebrospinal Fluid Sugar Mg. per 100 c.c.	Percentage Relation of Cerebrospinal Sugar to Blood Sugar	Amounts of Glucose Injected Gm.
L.	7/ 3/24	Encephalitis	Before	105	69	66	7.5
			2½ hours	132	80	61	
L. C.	10/ 4/24	Encephalitis	Before	91	57	63	12
			1 hour	143	58	41	
			2 hours	92	60	65	
			3 hours	60	65	108	
S. J.	5/28/24	Tuberculous meningitis	Before	108	14	13	12
			1 hour	138	18	13	
	6/ 2/24		Before	110	14	13	12
			1 hour	198	21	11	
			2½ hours	98	16	17	
H. S.	7/15/24	Tuberculous meningitis	Before	116	12	10	9
			3 hours	214	82	39	
I. W.	6/25/24	Tuberculous meningitis	Before	94	19	22	12
			3 hours	100	20	20	
D. R.	6/25/24	Tuberculous meningitis	Before	99	16	16	24
			2½ hours	98	50	51	
J. T.	6/25/24	Tuberculous meningitis	Before	102	29	28	12
			2¾ hours	226	84	36	
G. W.	8/ 1/24	Influenza meningitis	Before	69	Trace	--	15
		Postmortem	2 hours	71	Trace	--	

It is evident from these results that the injection or ingestion of glucose increases the cerebrospinal sugar, but

that no time can be set for the period of the maximum increase. These results indicate also that in meningitis the permeability of the meninges to sugar is not decreased, and that the decrease in the cerebrospinal fluid sugar is probably due to the lytic action of the cells and organisms present.

Cholesterol

Pighini found cholesterol in the cerebrospinal fluid of general paresis (88 per cent), of epilepsy (66 per cent), and of dementia precox (43 per cent). Chaufford, Laroche and Grigant and Weston found small amounts of cholesterol even in normal fluid. Pighini determined cholesterol qualitatively by the Liebermann method, while Chaufford, Laroche and Grigant and Weston determined it quantitatively.

In a series of fluids examined by Landenberger, Howell and myself, no cholesterol or only very minute traces were found in normal fluids. The method used by us was that of Bloor with slight modifications.

Fluid in which the Wassermann and Lange reactions were positive also contained no cholesterol in appreciable amounts. Only three out of 25 such fluids gave a reading in the colorimeter.

Fluid from cases of hemorrhage of the brain showed high cholesterol content ranging from 8 to 17 mg. of cholesterol per 100 c.c. of fluid.

Fluid from tumor of the brain gave a trace of cholesterol. Fluid from a case of brain abscess gave a high cholesterol reading, 13 mg. per 100 c.c. of fluid.

The majority of meningitic fluids showed a trace of cholesterol. Three fluids had a high reading.

Ventricular fluid gave no cholesterol reading, except when there was the presence of hemorrhage of the brain or other pathologic condition.

Lactic Acid

The lactic acid content of the cerebrospinal fluid has been shown by Glaser to be normal in syphilis of the central nervous system and to be increased in all forms of meningitis, and in some cases of brain tumor. Nishimura found an increase of 100 per cent in the lactic acid content of the cerebrospinal fluid in meningitis, tuberculous and meningococcic. Lactic acid was increased in the cases of suppurative meningitis that I examined.

Cholin

Mott and Halliburton found cholin in the fluid and sometimes also in the blood in cases of severe nervous lesions, especially in paresis. Donath found cholin in the fluid of epileptics and paretics, the largest amount being present in the latter. Gumprecht found cholin in the fluid of chronic meningitis. According to Mott and Halliburton normal fluid contains no cholin, although Gumprecht found traces of it in normal fluid. Kauffmann and Stanford found no cholin in the fluid of general paresis.

Acetone

Acetone was present in some of my cases after the fluid had been standing for several days. In a case of influenza meningitis there was a deep violet ring such as occurs in urine loaded with acetone. On a number of fluids from meningococcus meningitis the nitroprusside test for acetone gave a deep green ring. In diabetic coma, or other forms of severe acidosis, acetone may be present in the cerebrospinal fluid.

Bilirubin

Bilirubin may be present in the cerebrospinal fluid in severe jaundice and in some xanthochromic fluids due to old hemorrhage of the brain.

CYTOLOGICAL CHANGES

Any infection of the meninges gives rise to an increased number of cells in the cerebrospinal fluid. Often an irritation of the meninges will also cause an increase of cells in the fluid. Usually, the cellular increase and the protein

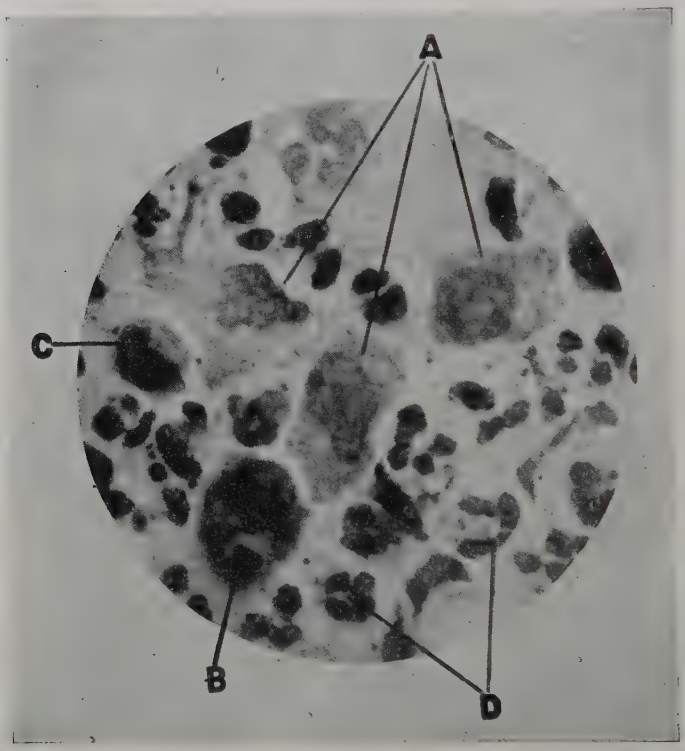

Fig. 45.—Photomicrograph showing types of cells in pathologic cerebrospinal fluid. x1000. *A*, desquamated endothelial cells. *B*, monocyte which has engulfed a polymorphonuclear leucocyte. *C*, large mononuclear cell. *D*, polymorphonuclear leucocytes.

increase run parallel. However, this is not always the case. During disease the cells differ as to their number and as to their origin according to the type and to the acuteness of the inflammation or of the irritation of the meninges. The following types of cells are found in pathologic cerebrospinal fluid. (Fig. 45.)

1. *Small lymphocyte.* (Small mononuclear leucocyte.)

This type of cell which is present in small numbers (1 to 6) in normal fluid and which is present in large numbers in tuberculous meningitis, poliomyelitis and luetic infections of the meninges, is the size of a red cell and contains a deeply staining nucleus, with one or two poorly defined nucleoli. The nucleus fills up nearly the whole cell. The small amount of remaining cytoplasm takes the Wright, Unna-Pappenheim or methyl blue stain less deeply than the nucleus and contains no granules.

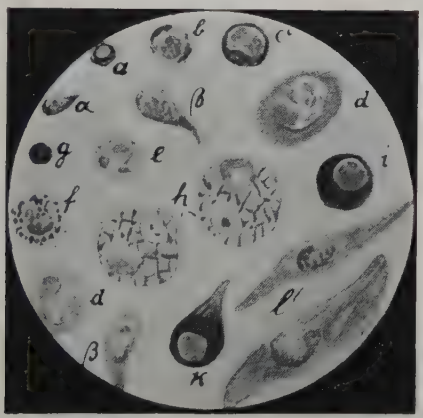

Fig. 46.—Cellular elements of cerebrospinal fluid. (Unna-Pappenheim stain.) *a*, small lymphocyte; *α*, small elongated lymphocyte; *b*, large lymphocyte; *β*, large elongated lymphocyte; *c*, transitional form to large lymphocyte with horseshoe-shaped nucleus; *d*, large lymphocyte with horseshoe-shaped nucleus; *e*, neutrophilic leucocyte; *f*, eosinophilic leucocyte; *g*, erythrocyte; *h*, "Gitterzell" or macrophage; *i*, plasma cell; *k*, elongated plasma cell; *l*, fibroblasts. (After Eskuchen.)

2. *Large lymphocyte.* (Large mononuclear leucocyte.)

This cell which is occasionally present in normal fluid may be present in large numbers in chronic inflammatory conditions of the meninges such as luetic affections of the meninges. The cell is twice the size of a red cell, and contains a round, less frequently oval, coarsely granular nucleus which fills up the large part of the cell and which stains deeply by the ordinary stain.

3. *Polymorphonuclear leucocyte.*

This type of cell is found in great numbers in all septic processes of the meninges, in meningeal hemorrhage and at times also in brain abscess. The cell varies in size, but is usually one and a half to two times the size of a red blood cell. The nucleus is subdivided into 2, 3 or 4 lobules and the cytoplasm contains many granules, the granules being either small and neutrophilic in character or large and eosinophilic. Most of the polymorphonuclear leucocytes found in the cerebrospinal fluid are neutrophilic.

Eosinophiles occur only rarely in the cerebrospinal fluid. They have been observed in cerebrospinal lues and also in chronic meningitides. Basophiles are hardly ever found in the cerebrospinal fluid.

4. *Monocyte.* (Transitional cell, endothelial leucocyte.)

This type of cell is said to be derived from the reticulo-endothelial system. It is larger in size than the large lymphocyte, being two or three times the size of a red blood cell. The nucleus fills about one-half the cell, and is lobated, indented or horseshoe-shaped, or less often, oval or round, and is eccentrically placed. The chromatin is arranged in a fine thready network; the relatively wide band of cytoplasm stains very lightly and is clear, although it may contain a few fine granules.

Monocytes may be present in the cerebrospinal fluid in cases of acute meningitis, especially meningococcus meningitis, and to a lesser degree in subacute inflammatory processes of the meninges.

5. *Plasma cell.*

This cell which is found in chronic processes such as general paresis, is the size of a large lymphocyte or a little larger. It contains coarse granules and a deep staining eccentrically placed nucleus, with radially arranged chromatin.

6. *Erythrocyte.*

In fluid from meningeal hemorrhage, in all acute inflammatory processes and whenever blood has been obtained

by an unsuccessful spinal puncture, red blood cells are found in the fluid.

7. *Fibroblast.*

This cell which is derived from connective tissue is present in chronic inflammation of the meninges. The cell body is elongated, pointed at both ends and contains a small round or oval nucleus.

8. *Desquamated endothelial cell.*

In all acute destructive processes of the meninges, desquamated endothelial cells in all stages of degeneration are found in the cerebrospinal fluid. The cells vary in size and shape. They are usually large, three to four times the size of a red blood cell. They are polygonal in shape and have a poorly defined border. The cytoplasm is pale and transparent and often contains vacuoles. The nucleus is large and takes the stain poorly. The presence of this type of cell indicates destruction of the meninges. They are especially numerous in meningococcus meningitis.

9. *Other degenerating cells.*

The "Gitterzell" of the German authors is a degenerated glia cell, the cytoplasm of which contains an increased amount of fatty substance, and is divided by many markings into its typical latticed appearance. According to Eskuchen, this cell has phagocytic properties, although this is doubtful. (Fig. 46.)

"Basket cells" are degenerated white blood cells and appear as large vacuolated leucocytes, or as mere strands of poorly stained nuclear material arranged in a coarse latticed network.

10. *Tumor and cyst cells.*

Sarcomatous cells may appear in the fluid of a case of sarcoma of the meninges. Echinococci have been found in the fluid from cases of echinococcic cysts. Sicard reported a case where actinomycotic granules were found in the fluid.

11. *Parasitic and fungus cells.*

Trichinae may occasionally be found in the cerebrospinal fluid in cases of trichinosis. In parasitic cystic infestation of the brain, the organisms may be present in the cerebrospinal fluid. Echinococci, cysticercus cells, yeast fungi, and actinomycotic granules have all been reported as being present in the cerebrospinal fluid.

Prognostic Value of Cytology of Cerebrospinal Fluid in Purulent Meningitis

A good deal has been written on the importance of the type of cell in cerebrospinal fluid in diagnosis, but there is very little material on the value of the type of cell in prognosis. The following may be of prognostic aid:

1. Prognosis is in reverse proportion to the cell count, the greater mortality occurring with the higher cell counts.
2. The presence of the desquamated endothelial cell usually speaks for a severe and destructive process of the meninges; whenever the endothelial cell persists the prognosis is therefore doubtful.
3. Change in the type of cells in the fluid from polymorphonuclear leucocytes to lymphocytes, usually indicates that the process is becoming subacute or chronic. The appearance of eosinophiles is a good prognostic sign.
4. In meningococcus meningitis there is often an abundance of cells and only few meningococci in the slide, while in pneumococcus meningitis the reverse may be true.
5. Whenever cells contain bacteria, especially meningococci, the prognosis is more favorable than when the organisms are outside of the cells.
6. Phagocytic cells in large numbers usually speak for a good prognosis.

ENZYMES

Catalase

As pointed out above, normal cerebrospinal fluid contains no catalase or only a negligible quantity of the enzyme.

TABLE LII

CATALASE IN TUBERCULOUS MENINGITIS AND POLIOMYELITIS

DIAGNOSIS	INTERVAL	READING	CELLS PER C.MM. AT TIME OF CATALASE DETERMINATION	OTHER TESTS
Tuberculous meningitis	5 hr.	9, 11	800 cells, 80% lymphocytes	Tubercle bacilli in fluid
Poliomyelitis	7 days in ice box	6, 6	13 cells	Chemical tests positive
Tuberculous meningitis	5 days	0, 0	No cells now; 110 lymphocytes immediately after removal from body	Tubercle bacilli found in fluid; globulin positive
Tuberculous meningitis	2½ days	3, 2	4 red cells, no white cells	Tubercle bacilli in fluid

Pathologic fluid does contain catalase enzyme, the amount depending on the number of cells present or on the presence or absence of a pellicle. (Tables LII and LIII.)

Diastase

Kafka found an increase in the diastase of the cerebrospinal fluid in meningitis. Eskuchen states that it is also increased in general paresis and dementia precox.

Other Enzymes

Kafka found lipase in the cerebrospinal fluid to be increased in syphilis of the central nervous system. He also found an autolytic ferment in general paresis. In purulent meningitis, Dochez and others demonstrated the presence of tryptic and proteolytic enzymes. Fibrin ferment is also present in meningitis.

BACTERIOLOGIC

Cerebrospinal fluid is sterile, even after it has passed through the nose as observed in the cases of rhinorrhea reported in the literature. Any bacteria in the fluid, are, therefore, indicative of the existence of some pathologic

TABLE LIII

CATALASE IN SUPPURATIVE MENINGITIS

DIAGNOSIS	INTERVAL	READING	CELLS AT TIME OF CATALASE DETERMINATION	OTHER TESTS
Meningococcus meningitis	½ hr.	14, 14	5,544 per c.mm. 90% polymorphonuclears	All bacteriologic and chemical tests positive
Meningococcus meningitis	4 days in ice box	6, 7	10 per c.mm.	All bacteriologic and chemical tests positive
Meningococcus meningitis after 90 c.c. serum	1 hr. at room temp.	20, 21	26 per c.mm.	Very high protein content; all other tests positive
Meningococcus meningitis	2 days	12, 12	.....	All tests positive
Meningococcus meningitis after 30 c.c. serum	5 days in ice box	19, 18	.....	All tests positive
Chronic basilar meningitis	4 hrs.	7, 7	100 per c.mm.	All tests positive
Meningococcus meningitis	19 days	6, 5, 6	.....	All tests positive
Meningococcus meningitis before serum	4 days	4, 5	No white cells	All tests positive
Streptococcus meningitis	24 hrs.	20, 20, 38*	2,000	Streptococcus in direct smear in great numbers; all tests positive
Streptococcus meningitis	3½ hrs.	40, 35, 65*	960	Streptococcus in great numbers; all tests positive

*The pellicle was included in these tests.

process in the body, unless it is known that the bacteria are the result of some external contamination of the fluid after having been removed from the body.

It is usually easy to find bacteria in the fluid of suppurating meningitis. However, at times it is very difficult to isolate bacteria from the fluid. Some bacteria, such as the pneumococcus and streptococcus grow easily on ordinary culture media; others, notably meningococci and influenza bacilli grow only on special media and at that with

difficulty, while still others, like the tubercle bacilli can hardly be grown at all, but must be detected by guinea pig inoculation. Almost any organism may cause meningitis, the most common being meningococcus, pneumococcus, streptococcus, staphylococcus, Spirocheta pallida, B. tuberculosis, B. coli, diphtheria, typhoid and anthrax bacilli. All of these and many others have been isolated from the cerebrospinal fluid.

IMMUNOLOGIC

Immunology has thrown a great deal of light on the diagnosis and pathology of diseases related to the nervous system. The various agglutination tests help to differentiate the various types of meningococci. The hemolysin reaction indicates a permeability of the meninges, and the Wassermann test is an invaluable aid in the diagnosis of syphilis of the nervous system.

Agglutination

The agglutination test is based on the principle that various bacteria agglutinate when they are brought into contact with their respective sera. This principle is utilized for the identification of meningococci and pneumococci.

Inhibition of Saponin Hemolysis

Hauptmann found that normal cerebrospinal fluid has no inhibitory effect on the hemolysis of red cells produced by saponin, while certain pathologic fluids, notably that of tumor of the brain, inhibit the saponin hemolysis of red blood cells. Table LIV shows Hauptmann's results.

Hauptmann considers the inhibitory action of pathological cerebrospinal fluid to be due to the increased amount of cholesterol in the cerebrospinal fluid produced by the degeneration of nervous tissue. Our work corroborates his contention. The technic of the test will be described in Chapter XIII.

TABLE LIV

Normal cerebrospinal fluid	No inhibition of hemolysis
Hemorrhage and softening of the brain of recent occurrence	85.7%
Hemorrhage and softening of the brain of long standing	No inhibition
Tabes	83% inhibition
Cerebrospinal lues	65% inhibition
Multiple sclerosis	46% inhibition
Epilepsy	No inhibition
Brain and cord tumor	100% inhibition

Hemolysin

Weil and Kafka demonstrated the presence of hemolysin or amboceptor and complement in the cerebrospinal fluid of certain affections of the central nervous system, especially where the meninges are involved. Normal cerebrospinal fluid, as pointed out in Chapter VII, contains no hemolysin. Weil and Kafka explain the presence of hemolysin in pathological cerebrospinal fluid, by the increased permeability of the meninges, a condition present in all forms of meningitis, and according to them also in tabes and in general paresis. These authors consider the hemolysin reaction of great diagnostic and prognostic significance.

Wassermann Reaction

Various views have been expressed in the literature as to the principle underlying the Wassermann test; Pighini thought it due to cholesterol, others thought it due to the presence of protective antibodies in the blood or cerebrospinal fluid. My own work does not confirm the idea of Pighini. The usefulness of the test, whatever the underlying principles, is very great.

Most authors consider a positive Wassermann test of the cerebrospinal fluid to be specific for syphilis of the central nervous system. Positive tests are reported to have been

found in the fluid of other conditions, such as leprosy and leishmaniasis, still it is practically pathognomonic of lues, especially in harmony with the clinical condition and the history of the case. A negative Wassermann, however, does not always rule out syphilis.

Toxicity

The cerebrospinal fluid of many pathologic conditions is toxic, notably the fluid of cases of tuberculous meningitis and epilepsy.

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CHAPTER XI

RELATION OF CEREBROSPINAL FLUID TO VARIOUS FACTORS

RELATION OF CEREBROSPINAL FLUID TO THE TIME OF DAY

Cavazzanni and Halliburton have shown that cerebrospinal fluid contains more total solids in the morning than in the evening. Cavazzanni suggests as an explanation of this finding, the hypothesis that during sleep the waste products of the brain are eliminated into the cerebrospinal fluid.

CHANGES IN CEREBROSPINAL FLUID WITH THE AGE OF FLUID

In normal cerebrospinal fluid which stands uncorked, the following changes occur: The P_H increases, the fluid becoming more alkaline. The sugar content is decreased, the decrease being greater at room temperature. The cells undergo autolysis. It is therefore necessary to perform the cell count on cerebrospinal fluid as soon as possible after its removal from the body. All these changes occur within the first twenty-four hours. After a period of several days, the fluid may change color, becoming slightly turbid. Finally, if allowed to remain exposed to the air for a long enough period, the fluid will all evaporate, leaving only a small residue of crystals.

In pathologic fluids, the same changes occur, but to a different degree. The cells degenerate more rapidly and the sugar content is diminished more quickly. However, the P_H remains constant or rises more slowly than does that of normal cerebrospinal fluid. If enough fibrinogen is present, a fibrin coagulum will form.

CEREBROSPINAL FLUID FROM DIFFERENT LOCI

Ayer and Solomon made a comparative study of cerebrospinal fluid from the lumbar, cisternal, and ventricular reservoirs. Table LV from an article by Freemont-Smith and Ayer, indicates the results of this comparative study for normal fluid. It is seen that the cerebrospinal fluid from the various loci are alike, with these exceptions: the ventricular fluid contains less cells and protein and more sugar than cisternal or lumbar fluid.

Under pathologic conditions, however, there may be marked differences in the cerebrospinal fluid from different loci. The manometric studies of cerebrospinal fluid pressure in different loci in conditions associated with subarachnoid block will be mentioned in the chapter on Methods of Withdrawal of Cerebrospinal Fluid. Table LV gives comparative findings in cerebrospinal fluid from different loci in brain tumor and in spinal subarachnoid block.

In general paresis, the cisternal and lumbar fluids are similar in all respects, except that the pleocytosis and globulin tests are not quite so marked in the cisternal as in the lumbar fluids. The ventricular fluid, on the other hand, may be entirely normal, even in regard to the Wassermann reaction. Generally speaking, all of the changes are less marked in the ventricular than in the lumbar fluid.

In cerebral hemorrhage, the cisternal and lumbar fluids usually contain blood. In intraventricular hemorrhages, the ventricular fluid contains blood, but in subarachnoid hemorrhage it does not.

Lewkowicz studied the cerebrospinal fluid from different loci in cases of suppurative meningitis. He found that the lumbar fluid contains a great many polymorphonuclear leucocytes, a great deal of protein and few organisms; the cisternal fluid contains less cells but more bacteria while the ventricular fluid contains many organisms and only few cells and little protein. These observations of the greater

TABLE LV

CEREBROSPINAL FLUID FROM DIFFERENT LOCI

	DISEASE	INITIAL PRESSURE: MM. OF SPINAL FLUID HORIZONTAL POSITION	RISE ON JUGULAR COMPRESSION	APPEARANCE	CELLS PER C.MM.	GLOBULIN	PROTEIN MG./100 C.C.	SUGAR MG./100 C.C.	CHLORIDES (AS NaCl) MG./100 C.C.	NON-PROTEIN NITROGEN MG./100 C.C.	GOLD SOL.	COMMENT
NORMAL	LUMBAR	70-190	Prompt	Clear	0-5	0	15-45	50-75	720-750	12-18	00000	Sugar and chloride values are for fasting nonfebrile patients.
	CISTERNAL			Colorless	0-5		10-25	50-75			00000	
	VENTRICULAR			No Clot	0-3		5-15	55-80				
BRAIN TUMOR												
ABOVE TENTORIUM — NOT INVOLVING WALL OF VENTRICLE	LUMBAR	+	N	N	N	N or slight increase	N or slight increase	N or +	N	N	Variable	Tumors involving optic chiasm may give increased cells (mononuclears). Lumbar puncture in patients with choked discs may be dangerous unless ventricle is tapped at the same time
	VENTRICULAR	+	N	N	N or slight increase	N	N	N or +	N	N	N	Ventricular fluid is normal
ABOVE TENTORIUM — INVOLVING WALL OF VENTRICLE	LUMBAR	+	N	N Occasionally faintly yellow	N or slight increase	+	+	N or +	N	N	Variable	Protein increase here comes from ventricle
	VENTRICULAR	+	N	N Occasionally faintly yellow	N or slight increase	+	+	N or +	N	N	Variable	Protein increase occurs in lateral ventricle invaded by tumor—other ventricle may have normal fluid
BELOW TENTORIUM — INTRACEREBELLAR AND FOURTH VENTRICLE	LUMBAR	+	N or Delayed	N	N	Slight increase or N	Slight increase or N	N or +	N	N	Variable	Fourth ventricle tumors usually do not cause any protein increase The protein increase below intracerebellar gliomas is slight, usually under 100 mg./100 c.c.
	VENTRICULAR	+	N	N	N	N	N	N or +	N	N	N	Ventricular fluid is normal—subtentorial block is best demonstrated by combined ventricular and lumbar puncture
BELOW TENTORIUM — EXTRACEREBELLAR	LUMBAR	+	N or Delayed	N or faintly yellow Rare clot	N	+	+	N or +	N	N	Variable	Protein increase in these cases is well marked. Usually 150 mg./100 c.c. or higher
	VENTRICULAR	+	N	N	N	N	N	N or +	N	N	N	Ventricular fluid is normal

TABLE LV—CONT'D

	DISEASE	INITIAL PRESSURE: MM. OF SPINAL FLUID HORIZONTAL POSITION	RISE ON JUGULAR COMPRESSION	APPEARANCE	CELLS PER C.MM.	GLOBULIN	PROTEIN MG./100 C.C.	SUGAR MG./100 C.C.	CHLORIDES (AS NaCl) MG./100 C.C.	NON-PROTEIN NITROGEN MG./100 C.C.	COLD SOL.	COMMENT
SPINAL SUBARACHNOID BLOCK (TUMOR, POTTS DISEASE, MENINGITIS, ETC.)												
PARTIAL BLOCK	LUMBAR	N or Low	Delayed	N or faint yellow Clot rare	±	+	+	N	N	N	Variable	Partial block is best demonstrated by combined cistern and lumbar puncture
	CISTERNAL	N	Prompt	N	±	N	N	N	N	N	Variable	Lipiodol arrest, but some passes by the block
COMPLETE BLOCK	LUMBAR	Low or N	Absent	Colorless with slight clot, to deep yellow with massive coagulation	±	++	+++	N	Slightly low	N	Variable	Little fluid obtainable. Rapid drop in pressure to zero
	CISTERNAL	N	Prompt	N Faint yellow color or clot rare	±	±	±	N	N	N	Variable	Cistern puncture not necessary to demonstrate block Lipiodol completely arrested
TUMOR OF CAUDA EQUINA	LUMBAR (below tumor)	Low	Absent or Delayed	Colorless with slight clot, to deep yellow with massive coagulation	N	++	+++	N	—	—	Variable	
	LUMBAR (above tumor)	N	Prompt	Yellow or colorless, clot ±	N	+	++	N	—	—	Variable	
	CISTERNAL	N	Prompt	N Yellow color or clot rare	N	±	±	N	—	—	Variable	
Radiculitis of cauda equina also numerous cases of acute polyneuritis		N	N	N or yellow Clot ±	±	+ to ++	+ to +++	N	N or Slightly low	N	Variable	Radiculitis of cauda equina difficult to distinguish from tumor, unless puncture is below lesion and block can be excluded. Lipiodol valuable

number of organisms in the ventricular fluid have led Lewkowicz to the supposition that in purulent meningitis the organisms reach the cerebrospinal fluid through the chorioid plexus and that therefore the intraventricular administration of serum is indicated in these cases. In tuberculous meningitis, Ayer and Solomon found more cells and organisms in cisternal than in lumbar fluid.

From a diagnostic standpoint removal of fluid from different loci is valuable mainly in suspected subarachnoid block.

POSTMORTEM CHANGES IN CEREBROSPINAL FLUID

It is often desirable to examine cerebrospinal fluid obtained postmortem, either in cases of sudden death, before fluid could be obtained antemortem, or for purposes of obtaining sufficient fluid for experimental work. Naturally the question arises whether or not information obtained from postmortem fluid is valid for antemortem conditions also. Many changes occur in normal and pathologic cerebrospinal fluids after death, and the discrepancies between the results of the older and the more recent workers on cerebrospinal fluid may be attributed to the fact that the former worked with fluid obtained postmortem to a great extent.

In general, it may be stated that greater changes occur postmortem in pathologic fluids than in normal fluids. In normal fluids, the changes are mainly chemical, and according to Cohen may be due to a postmortem increase in the permeability of the meninges. The following changes occur in normal cerebrospinal fluid after death:

1. Inorganic phosphates rapidly increase, according to Cohen.
2. Magnesium content rapidly increases, as a result, according to Cohen, of a corresponding increase in

the magnesium content of the blood, and of nervous tissue autolysis.

3. Calcium content rapidly increases according to Critchley and O'Flynn.
4. Nonprotein nitrogen increases.
5. Chlorides are decreased.
6. Cholin appears in the cerebrospinal fluid very quickly, probably due to nerve tissue destruction.
7. Potassium oxide rapidly increases according to Myers.
8. The P_H decreases so that postmortem the fluid becomes acid in reaction instead of alkaline.
9. The pressure usually falls to zero so that the fluid may have to be aspirated. In some cases, however, the pressure may remain at the antemortem level and fluid may be removed by means of a spinal puncture needle without aspiration.
10. Peptolytic ferment increases according to Mandelbaum as quoted by Eskuchen.
11. The color remains clear, globulin tests are negative and the cell count is normal for at least 30 days according to Eskuchen. After a longer period, the fluid may become turbid and the globulin reaction positive.
12. The fluid usually remains sterile after death according to Eskuchen. I have found many colon bacilli in postmortem fluids obtained from cases in which there was no meningeal involvement. This leads me to believe that postmortem fluid is often invaded by the colon bacillus soon after death.

In pathologic fluids the same changes occur postmortem as in normal fluids, except that they occur more rapidly. In addition, however, cytologic and bacteriologic changes occur.

In tuberculous meningitis according to Eskuchen, there is a marked increase in the number of macrophages and

tubercle bacilli in the cerebrospinal fluid postmortem. These changes, he believes, begin just before death and continue even after death and are characteristic of this condition. In diphtheria, before death the cerebrospinal fluid contains no organisms, but postmortem the diphtheria bacillus appears in the cerebrospinal fluid, according to Leede as quoted by Eskuchen. The reverse occurs in epidemic meningitis, wherein during life the viable organisms are plentiful, but following death the fluid may become devoid of bacteria.

The Wassermann and colloid reactions are not altered in postmortem fluid.

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CHAPTER XII

METHODS OF OBTAINING CEREBROSPINAL FLUID FROM THE LIVING BODY

Before the days of spinal puncture the removal of cerebrospinal fluid from the living body was effected with a great deal of difficulty. The usual method of removing cerebrospinal fluid from dogs was by means of a fistula between the occiput and the atlas. From human beings cerebrospinal fluid was obtained through an accidental flow of fluid from the nose or ears. Another way of obtaining cerebrospinal fluid from the living body, but one used only very rarely, was an open operation either on the head or on the vertebral column.

A number of methods have been used since 1891, the year Quincke described spinal puncture, for the removal of fluid from human beings. Cazaman removed fluid from the cisterns by inserting the needle below the eye, using the sphenoidal route. Cushing and Haynes drained cerebrospinal fluid by the open occipito-atlas route. Wegeforth, Ayer and Essick in 1919 punctured the cisterna magna by means of a needle. Chartier punctured the eighth dorsal space, a method employed by Corning as far back as 1885.

Of all the methods described, lumbar puncture is the method of choice. In infants, before the closure of the anterior fontanelles, ventricular puncture is a more desirable method of obtaining fluid than cistern puncture. After closure of the fontanelles, cistern puncture naturally is to be used as ventricular puncture would necessitate trephining.

LUMBAR PUNCTURE

Lumbar puncture is an operative procedure. It not only necessitates piercing the skin, fascia, muscle, ligament and dura mater, but it disturbs the equilibrium of the spinal canal by the withdrawal of fluid from the canal. It has also been shown that simple aspiration of a large quantity

of fluid produces a transient irritation of the meninges. This irritation which was observed by Kasahara on rabbits, also applies to human beings. It should therefore be done only when there is a proper indication for it. However, when indicated, no fear of possible untoward effects should prevent one from doing a lumbar puncture.

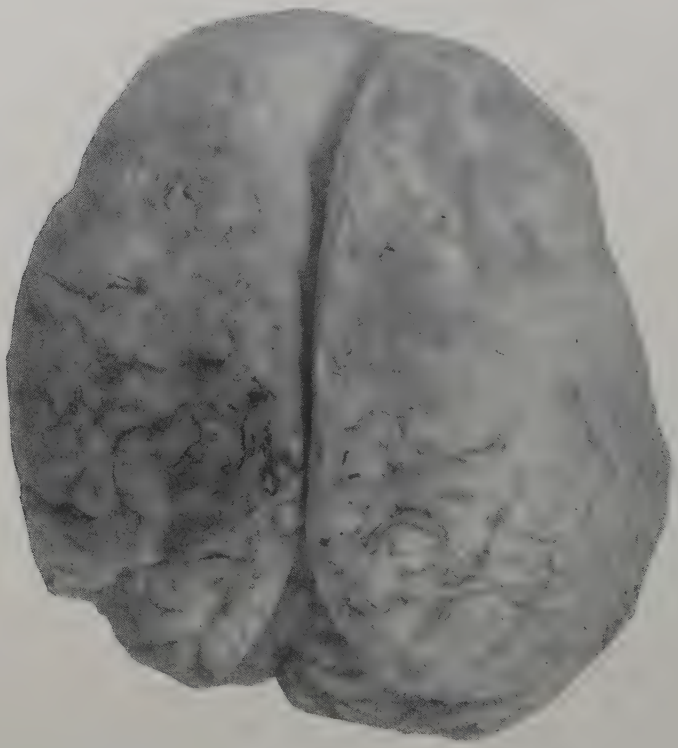

Fig. 47-*A*.—Specimen illustrating the importance of spinal puncture for diagnostic purposes. S. C. entered the hospital with symptoms of pneumonia and with marked cyanosis. At first sight there seemed to be no indication for a spinal puncture, but when convulsions set in, a puncture was done. The fluid withdrawn was very turbid and showed pneumococci in direct smear as well as in culture. The postmortem showed a well-defined exudate of the meninges, the exudate containing many pneumococci.

Indications

The first lumbar puncture by Quincke in 1891 was done for therapeutic purposes. Since that time, however, we

have learned a great deal about the value of lumbar puncture for diagnostic as well as for therapeutic purposes. Therapeutically, lumbar puncture is done for the relief of increased intracranial pressure as in hydrocephalus, delirium tremens, encephalitis, eclampsia, and allied conditions. Of great value is lumbar puncture for the purpose of injecting serum in cases of purulent meningitis, for the

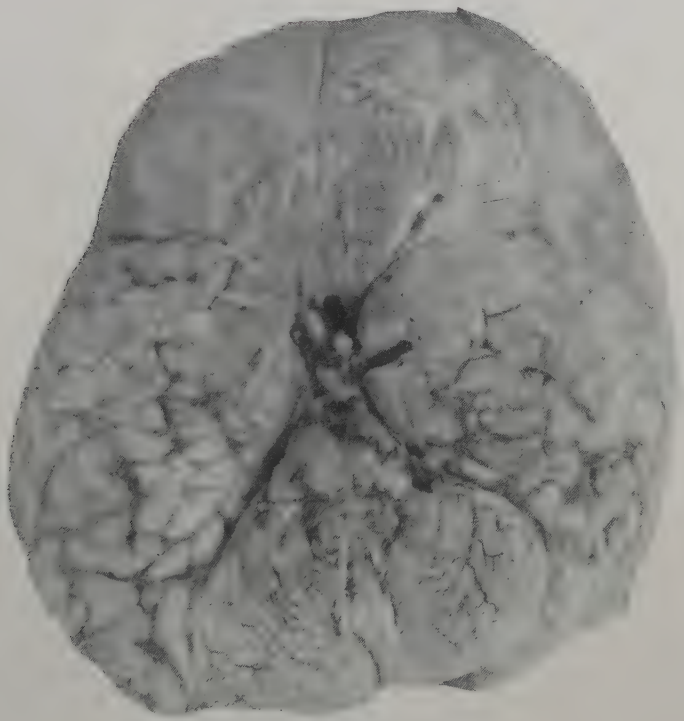

Fig. 47-*B*.—Opposite view of Fig. 47-*A*.

intraspinal treatment of neurosyphilis and tetanus and for spinal anesthesia. Lumbar puncture has also been employed by some for the relief of general edema in cases of nephritis. Several cases are reported of meningeal hemorrhage which recovered after lumbar puncture. Improvement by spinal puncture has also been reported in two cases of diabetes insipidus. As a general rule, a spinal puncture should be made in all cases showing signs of in-

creased intracranial pressure with the possible exception of subtentorial brain tumors.

Diagnostically, lumbar puncture is of great value in such conditions as cerebrospinal lues, hemorrhage of the brain, tumors of the cord, poliomyelitis, and meningitis. It is particularly valuable in the diagnosis of all forms of meningitis and poliomyelitis. The following cases are cited to show how important a diagnostic measure spinal puncture may be:

S. C. entered the hospital with symptoms of pneumonia and cyanosis. The lung findings were indefinite. There was very little rigidity of the neck and no other symptoms pointing to meningitis. At first sight there seemed to be no indication for a spinal puncture, but when convulsions set in a puncture was made. The fluid withdrawn was turbid and showed pneumococci in smear and culture. The necropsy showed the lungs to be congested, but no pneumonia was present. The cerebrum, however, was covered with a gelatinous, greenish gray, purulent material several millimeters thick and very firm; the exudate was located on the upper and lateral surfaces of the brain. (Figs. 47-*A* and *B*.) The smears as well as the cultures showed gram-positive cocci.

Although in this case not much could have been done therapeutically even if the process had been recognized earlier, the spinal puncture was of great value. It served to establish a positive diagnosis in a case in which a meningeal exudate existed with few if any of the meningeal symptoms that usually accompany such a condition.

The case that follows illustrates even more vividly the importance of lumbar puncture:

S. W., ten years old. Sick for five days. Complained of pain in lumbosacral region, and also in the right hip, radiating to the sole of the foot at times; occasionally there was pain in the left shoulder. When first seen the temperature was 102° F. There was tenderness to touch in the lumbosacral and gluteal regions, slight rigidity of the neck, slight Kernig and contralateral Brudzinski signs. The diagnosis by several physicians was neuritis. On lumbar puncture a very turbid fluid was obtained under great pressure. Bacteriologic examination showed meningococci and several hundred cells per cubic millimeter. All globulin tests were positive. The patient was given several doses of antimeningococcus serum and recovery followed.

In this case lumbar puncture was a life-saving measure. In the next case meningitis could hardly have been discovered without lumbar puncture as the general symptoms were so indefinite.

F. R., aged eight months. Sick one day with fever and constipation. Had attack of cyanosis for a few minutes. General examination was negative. Lumbar puncture was done and to the great surprise of the physicians, the fluid was found very turbid and full of meningococci.

These cases are but few of a great number coming under my observation that illustrate the extreme importance of lumbar puncture. It is well known that many cases of convulsions are relieved by no other procedure than lumbar puncture. The following outline summarizes the most important indications for lumbar puncture:

Indications for Lumbar Puncture

For Diagnosis
- Suspected meningitis
- Suspected poliomyelitis
- Suspected encephalitis
- Hemorrhage of the brain
- Neurosyphilis
- Coma
- Convulsions
- Paralysis
- Injection of air or lipiodol

For Treatment

(a) Relief of intracranial pressure
- Meningitis
- Meningism
- Poliomyelitis
- Encephalitis
- Hemorrhage of the brain
- Delirium
- Convulsions
- Hydrocephalus
- Uremia

(b) Intraspinal injections

1. Serum treatment
   - Antimeningococcus
   - Pneumococcus serum Type I
   - Streptococcus
   - Influenza
   - Poliomyelitis
   - Tetanus antitoxin
   - Horse serum
   - Swift-Ellis treatment
2. Chemicals
   - Neo- or sulpharsphenamine
   - Tryparsamide
   - Mercury
   - Optochin
   - Magnesium sulphate
   - Novocain-procaine-apothesin
   - Adrenalin
   - Mercurochrome

(c) Miscellaneous
- General edema
- Diabetes insipidus
- Uremia

Contraindications

There are very few contraindications to lumbar puncture. In cases of tumors of the cerebrum and cerebellum, it is true that puncture is not so safe as under ordinary conditions. Even then, however, a lumbar puncture may be done with little trepidation if the pulse and reflexes of the patient are watched and if only a small amount is removed and the pressure of the cerebrospinal fluid is measured.

In erysipelas or abscess of the lumbar region lumbar puncture is contraindicated, as the infection may be carried by the needle into the spinal canal. In this case a ventricular or cistern puncture should be done. In the exanthemata, such as scarlet fever, measles or chickenpox, spinal puncture should be done only when absolutely necessary for diagnostic or therapeutic purposes.

Reactions Following Removal of Cerebrospinal Fluid

The enthusiastic reports which followed Quincke's description of spinal puncture were followed in the last few years by a reaction on the part of some clinicians against the removal of cerebrospinal fluid from the body. The cause of the fear is mainly (1) the occasional report in the literature of death following spinal puncture, (2) of leakage of cerebrospinal fluid following spinal puncture, and (3) the statement that in cases of pneumonia, spinal puncture may precipitate a meningitis. Other dangers attending spinal puncture include puncturing of the aorta, nerve injury and breaking of the needle.

The following transitory reactions have been observed by me following lumbar puncture:

1. Headache.
2. Oozing of cerebrospinal fluid from puncture wound.
3. Radiating pains to the thighs.
4. Edema of skin in lumbar region.

5. Rigidity of neck.
6. Rise in temperature.
7. Twitching.
8. Inability to sit up.
9. Purpura, localized and generalized.

Deaths resulting from spinal puncture have been reported. These, however, usually occurred in cases of brain tumor. Of the many hundreds of punctures that have come under my observation I have seen only two cases of death following puncture. One of these was a case of brain tumor, and the other of brain abscess. In the latter a depression was found around the base of the cerebellum, undoubtedly due to herniation of the brain through the foramen magnum. The report of the case follows:

R. H., eight years old, was admitted to the Sarah Morris Hospital November 21, 1926, with a history of headache of two weeks' duration, vomiting one week, drowsiness four days' duration, unconsciousness for four days, and convulsions one day. Three weeks before admission the patient had an earache for which she was treated.

On admission to the hospital the patient was in a state of convulsion, with retraction of the head. Examination after the convulsion subsided revealed an internal strabismus of the right eye, inequality of the pupils (left larger than the right), rigid neck, and positive Brudzinski. Tuberculous meningitis, brain abscess, and encephalitis were considered in the diagnosis.

A lumbar puncture was done and 8 to 10 c.c. of clear fluid were removed under greatly increased pressure. As soon as the canal was entered, the patient took three or four very deep, sighing respirations, and then resumed her previous respirations. A few minutes afterward, however, the patient began having respiratory difficulty, became cyanotic, and died.

The necropsy, done one hour after death revealed an abscess in the outer half of the right lobe of the cerebellum. In addition it was found that around the base of the cerebellum there was a depression about 1 cm. deep, that portion which rested on the border of the foramen magnum being sharply angulated. The two surfaces of the depression came together at an angle of about 50 degrees. About this region there was a quantity of extravasated blood, and when the brain was removed some of the blood was seen to be under the arachnoid (Fig. 48).

I believe that when lumbar puncture is done with the patient sitting up, death may result from the production of cerebral hernia, by release of the fluid at the base of

the brain. This may, in part, at least, explain some of the deaths reported in the literature.

I have never seen a meningitis develop following a spinal puncture done in a case of pneumonia which I could attribute to the puncture.

Piercing of the aorta is a very rare occurrence, and when it does happen it is due to poor judgment on the part of

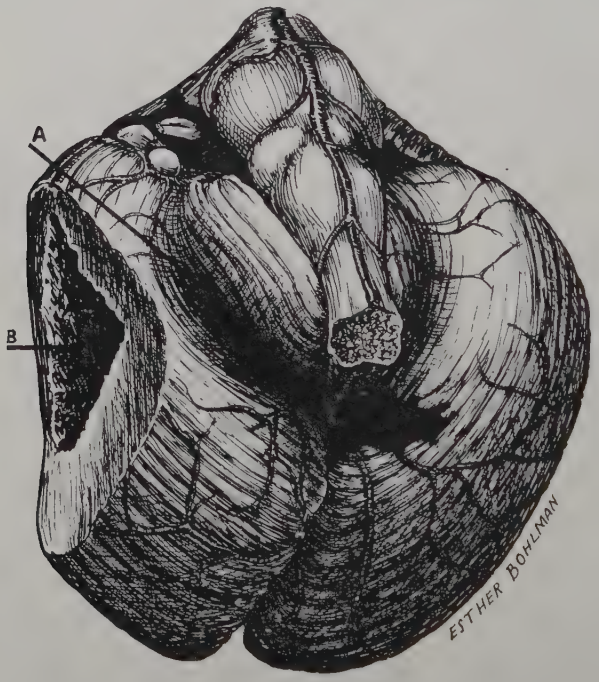

Fig. 48.—Herniation of the brain following lumbar puncture. *A*, indicates pressure groove; *B*, abscess.

the operator as to the depth to which the needle should be introduced.

Injury to the nerves is a complication that can easily be averted if the puncture is made at a low level in the lumbar region, preferably between the third and fourth vertebræ.

Breaking of the needle may result from undue force. If the needle is broken directly beneath the skin, it is best to incise the skin and remove it. If it is broken deeper, how-

ever, which is generally the case, it is best to let it alone for a while. If no complications occur in several days, it is advisable to leave the needle inside. If severe pain or suppuration occurs, the needle should be removed by operation.

The cause of headache after lumbar puncture is a matter of speculation. It is generally attributed to the removal of too great an amount of fluid at one sitting. Headache, however, sometimes follows even after the removal of a small amount of fluid. MacRobert has suggested that headache following lumbar puncture may be due to the nonclosure of the puncture hole in the arachnoid. The arachnoid tissue in a case of this kind, the author says, is pulled through the dural opening when the needle is withdrawn. This results in prolonged epidural leakage and in the lack of support of the medulla, a condition which gives rise to severe headache. This explanation is rather plausible in view of the fact that occasionally cerebrospinal fluid continues to ooze from the puncture wound after withdrawal of the needle. Solomon believes that headache following lumbar puncture is due to a decrease in cerebrospinal pressure. He advises the injection of 1 c.c. of pituitary extract intramuscularly to raise the cerebrospinal pressure. In 1923, Depisch and Richter-Quittner stated that the probable cause of postlumbar-puncture headache was associated with a decrease in the calcium content of the cerebrospinal fluid and advised the administration of calcium lactate by mouth prophylactically to prevent its occurrence. Their results, however, have not been corroborated by the work of Critchley and O'Flynn and of Neustaedter, Hala and Tolstoouchow. Postlumbar-puncture headache is more likely to occur in normal persons than in those having pathologic fluids. According to Pardee, it occurs more often in multiple sclerosis than in any other condition.

When headache does occur after lumbar puncture the best method of treatment is to put the patient flat on his

back for several hours. Occasionally it becomes necessary to resort to drugs for relief of the condition. Sodium and potassium bromide or salicylates may then be employed. Rarely is it necessary to use stronger remedies than these. Occasionally the headache may persist for several days and even weeks.

Pain in the extremities after lumbar puncture is usually due to injury of one of the filaments of the cauda equina. Rest in bed is usually all that is necessary to relieve this condition.

Edema of the skin in the lumbar region is an infrequent complication. I have seen it after repeated punctures. When it does occur, the lumbar region should be given a rest and if necessary to introduce serum, it should be injected into the ventricles or into the cisterna magna. When edema of the skin occurs, warm cloths should be applied to the edematous region and serum given by another route until the edema subsides, after which intraspinal introduction of serum may be resumed.

Rigidity of the neck, twitching, inability to sit up, and rise in temperature which may follow lumbar puncture may be the clinical evidences of the meningeal irritation which occasionally follows removal of cerebrospinal fluid.

Localized or generalized purpura or petechiae following lumbar puncture occurs occasionally in a purulent meningitis. This phenomenon may possibly be due to a septicemia caused by some of the purulent fluid entering a blood vessel ruptured in the course of the puncture.

In general, lumbar puncture when indicated should not be feared because of complications.

Technic of Lumbar Puncture

To do a spinal puncture properly one must take into consideration a number of important factors.

1. The anatomic relations of the cord and its membranes at the lumbar region.

The cord, in the adult, ends at the first lumbar vertebra, and in the child, at the second vertebra, seldom at the third. The cord has its ending in the conus medullaris, the apex of which is continuous with the filum terminalis. Throughout its entire length the cord is surrounded by three membranes, the dura, the arachnoid and the pia. The accompanying drawing (Fig. 49) shows the membranes surrounding the cord and the cauda equina in a dog. The same relations also hold good in man. Of importance also is the anatomic fact that the third lumbar interspace in the adult is the widest and therefore the site of choice for lumbar puncture.

2. The structures encountered between the skin and the cord, which are as follows from without inward:

(a) Skin.
(b) Subcutaneous fascia.
(c) Fat.
(d) Deep fascia.
(e) Multifidus muscle.
(f) Vertebral arches.
(g) Ligamentum flavum.
(h) Dura.
(i) Arachnoid.

3. The plexus of veins on the posterior wall of the body of the vertebra (Fig. 50). If these are struck by the spinal puncture needle the resultant fluid is bloody.

Another matter for consideration in lumbar puncture is the position of the patient, particularly if the patient is a child. While in an adult the physician may do the puncture with the patient in either the sitting or reclining position, in a child he should not attempt the puncture with the patient in any but a reclining posture.

Glaser was more successful in obtaining fluid from prematurely born infants when the puncture was done with the patient in the sitting position. It is true that the danger of herniation of the brain is not great in premature

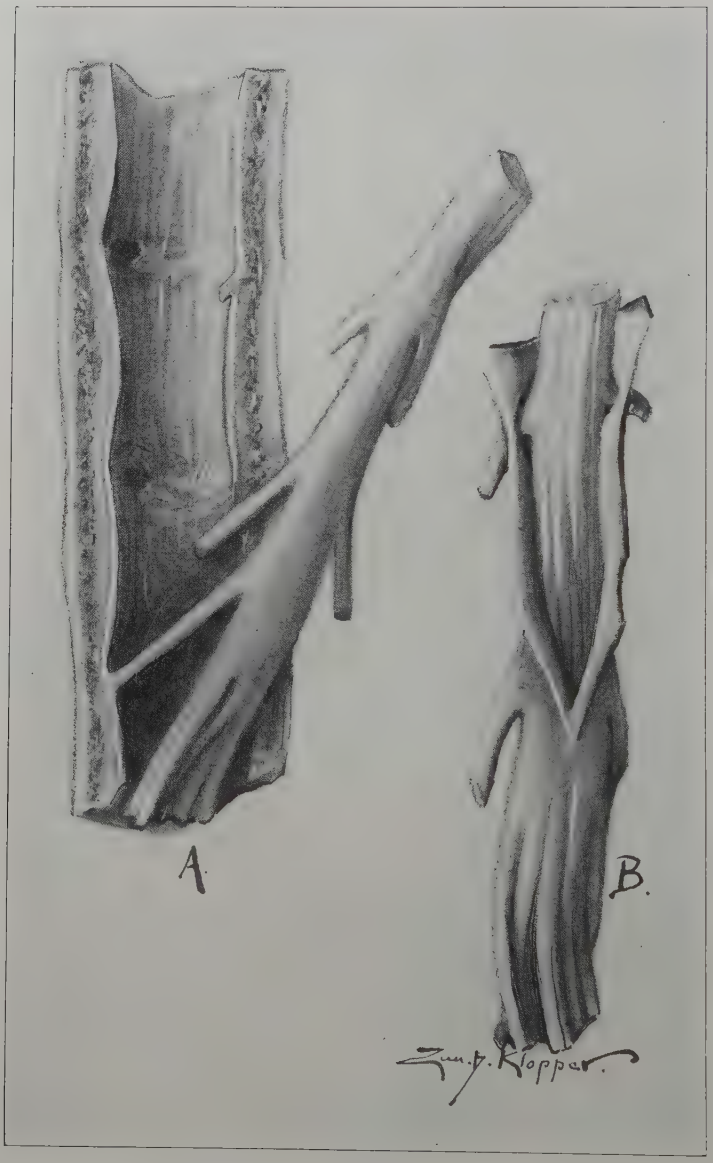

Fig. 49.—Section of cauda equina of a dog. *A*, Membranes intact; *B*, Dura and arachnoid cut open.

infants due to the fact that the amount of fluid in all newborn, especially those born prematurely, is very small and the pressure very low. It is, however, safer to do it in the recumbent posture.

In all cases of meningitis the patient should be in the lying posture when the puncture is performed. The patient may be placed on either right or left side, the right being preferable, and his back should be arched so as to widen the intervertebral spaces.

The skin should be prepared very carefully for the puncture. Soap and water, alcohol and iodine should be used for cleansing purposes. Rubber gloves should be worn and

Fig. 50.—Plexus of veins, the puncture of which is responsible for blood obtained during spinal puncture. (Gray's Anatomy.)

all other aseptic precautions must be taken to minimize the danger of infecting the meninges. As a rule neither a general nor a local anesthetic is called for in doing a spinal puncture. It may be necessary to resort to an anesthetic in maniacal cases, although I have not encountered a single case in which I could not get along without it. Should a general anesthetic become necessary, chloroform should be the anesthetic of choice. Sophian suggests that the patient be given water to drink during lumbar puncture. He found that this procedure made an anesthetic unnecessary. As a rule, however, even this is not necessary.

Quincke's advice that the needle be introduced directly

in the midline in children and 5 to 10 mm. to one side of the midline in adults, holds good to this day. In adults the needle is preferably inserted in the third or fourth interspace, so as to avoid the possibility of injury to the nerves. A good landmark for the guidance of the needle may be made by drawing a horizontal line through the vertebral column across the crests of the ilium. I usually draw this line with tincture of iodine on a swab. This strikes the interspace between the third and fourth vertebra.

It is often quite difficult to feel the intervertebral space in fat persons and in very young children. Because of this difficulty extreme care is necessary in cases of this kind.

In infants and children it is generally advisable to use a smaller needle and to go in one to two interspaces higher.

The needle, being inserted to one side of the midline, is forced into the interspace and then directed slightly upward and forward.

When the needle passes the dura, a snap is felt. The stylet should then be removed slowly so as to prevent a sudden gush of fluid, and the fluid allowed to run into the pressure apparatus or into the collecting tubes.

After the needle is withdrawn, the skin should be washed off with alcohol if iodine had been applied before the puncture, and collodion should be put on the wound. The patient should be put to bed flat on his back immediately after the puncture to prevent headache or dizziness.

The usual increase in cerebrospinal fluid sugar on injection or ingestion of glucose would speak for the inadvisability of performing spinal puncture when cerebrospinal fluid sugar determination may be of value, one to three hours after ingestion of glucose or after any meal which contains carbohydrates. If the patient is not acutely ill, it is best to do the spinal puncture in the morning, after a night's fast. However, if the delay of the spinal puncture may delay the injection of serum or otherwise interfere with either the diagnosis or treatment, the food

factor may be disregarded. If the fluid is to be examined for the Wassermann reaction, it should not be taken within two to three days after an alcoholic debauch, as the presence of alcohol in the cerebrospinal fluid may change a positive Wassermann reaction to a negative one.

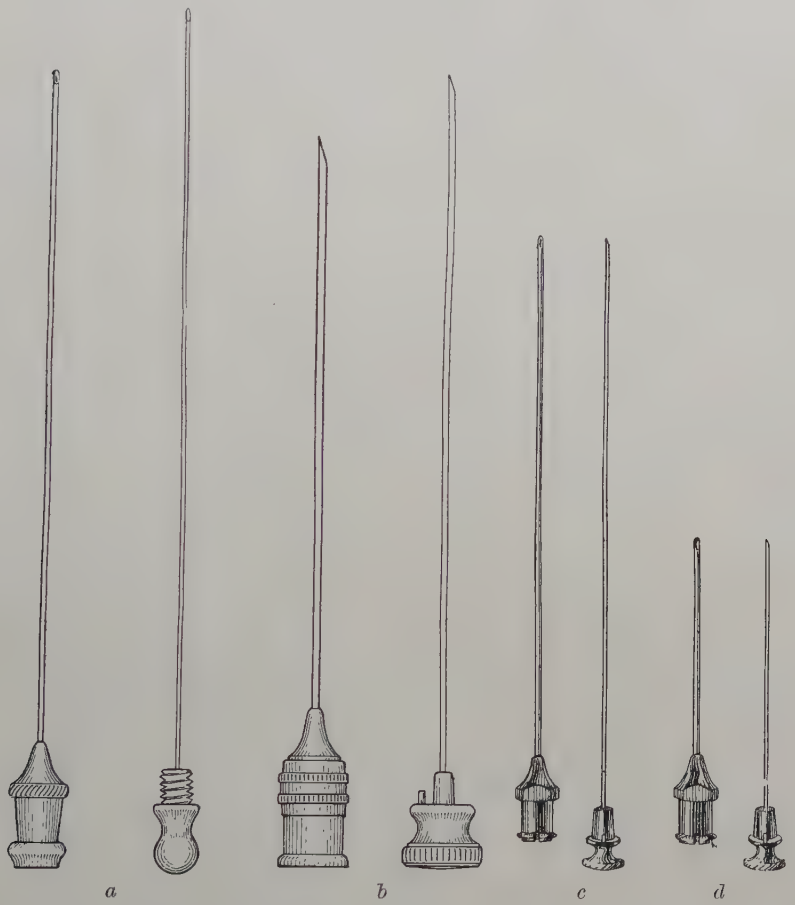

Fig. 51.—Various types of lumbar puncture needles. The pin locks of needles *b*, *c*, and *d* are more practical than the screw lock of needle *a*. Needle *d* is useful for spinal puncture in infants.

The Spinal Puncture Needle

Regular spinal puncture needles are now made measuring from 7 to 9 cm. in length and 0.6 to 1.2 mm. in thickness with a stylet to fit the needle (Fig. 51). Some needles

are made with valves for the measurement of the pressure of the fluid. Most needles on the market are made of steel, although some are nickel-plated and some made of platinum iridium. If meningitis is not suspected a needle with a small lumen will do, but if there is the slightest suspicion of meningitis a needle with a large lumen should be used as the fluid may be purulent and thick enough to clog the needle. The needle should be boiled and cooled before using. It should also be examined very closely for rust.

"How much of the needle should be introduced into the canal?" is one of the first questions that greets the inexperienced operator. In consulting literature on the subject I found very little information about the length of the needle, the only tabulated data available being by Quincke, who, however, cites only a few cases. (Table LVI.)

I measured the length of the needle in a series of several hundred cases, adopting the following procedure: When

Table LVI

Measurements by Quincke

AGE	DEPTH
1⅓ years	2.0 cm.
7 "	2.5 "
	3.0 "
	3.0 "
	2.7 (3.5) cm.
	3.2 "
2 "	2.5 "
1¼ "	2.0 "
25 "	1.5 "
	6.0 "
	6.5 (4.7) "
39 "	5 plus "
22 "	5.2 "

ready to remove the needle from the spinal canal after obtaining a good flow of fluid, I grasped the needle close to the patient's skin between the thumb and index finger,

pulled it out, and measured it from the point held by the fingers to the tip.

Table LVII gives the measurements of the needle made in children from four months to twelve years of age and Table LVIII gives the measurements in adults of various ages. I included here but a few of the several hundred of measurements made. In cases in which the results were similar I

TABLE LVII
MEASUREMENTS OF NEEDLE IN CHILDREN

NO.	AGE	LENGTH OF NEEDLE IN CM.
1	4 months	2.0
2	5 "	2.2
3	6 "	2.0
4	6 "	2.3
5	6 "	2.5
6	7 "	2.5
7	8 "	2.4
8	9 "	2.2
9	12 "	2.2
10	12 "	2.0
11	14 "	2.8
12	14 "	2.5
13	21 "	3.5
14	22 "	3.0
15	2 years	2.7
16	2 "	2.1
17	2 " 7 mo.	2.4
18	3 "	4.0
19	3 "	2.0
20	3 "	2.8
21	3 "	2.9
22	4 "	3.2
23	4 "	2.9
24	4 "	2.8
25	5 "	3.2
26	6 "	3.0
27	7 "	4.0
28	8 "	3.5
29	8 "	3.5
30	9 "	3.7
31	9 "	3.4
32	9 "	4.0
33	9 "	3.8
34	10 "	3.6
35	12 "	3.2
36	12 "	3.6

tabulated but one measurement; in cases of the same age where the measurements were different several measurements are tabulated. In some cases the results of several measurements are given for the same patient to show the length of the needle at different punctures. As is seen from the table, the depth of the needle varies from 2.0 to 4.0 cm. in children up to twelve, and from 4.1 to 10 cm. in people over sixteen years of age. The variations in the adult may be attributed to several factors. Obesity and muscular development is one; the direction taken by the operator in inserting the needle is another, an oblique insertion naturally requiring a greater length of needle than a straight insertion. The location of the interspace is another factor, the higher the point of insertion, the greater being the length of the needle introduced. Some clinicians use as the place of introduction the space between the third and fourth lumbar vertebrae, others the space between the second and third. It is also interesting to note that the length of needle inserted varies at different punctures in the same patient. This is due to the fact that the canal is quite wide and that fluid may be removed whether the needle is near the anterior or near the posterior surface of the canal.

Failure to Obtain Fluid

There are times when no fluid can be obtained in spite of all efforts. Among the factors responsible for the failure to obtain fluid, the most important are the following:

1. The needle may not have been inserted far enough into the canal.

2. The needle may have been introduced too far into the canal. In such cases the material exuding from the intervertebral disc may clog up the needle.

3. There may be a thickening of the exudate in the spinal canal so that it cannot pass through the lumen of the needle. This happens occasionally in cases of suppurative meningitis.

TABLE LVIII

MEASUREMENTS OF NEEDLE IN ADULTS

NO.	AGE	LENGTH OF NEEDLE IN CM.
1	16 years	5.4
2	20 "	4.8
3	25 "	5.0
4	26 "	5.3
5	27 "	5.8
6	29 "	4.9
7	29 "	5.5
8	30 "	5.6
9	30 "	4.5
10	30 "	5.4
11	30 "	5.2
12	30 "	5.8
13	30 "	5.6
14	31 "	5.5
15	31 "	10.0 (very fat)
16	32 "	5.1
17	33 "	4.1
18	33 "	5.1
19	34 "	5.1
20	34 "	5.2
21	34 "	4.5
22	34 "	4.6
23	35 "	5.7
24	35 "	4.8
25	35 "	5.5
26	36 "	4.1
27	37 "	5.3
28	37 "	5.5
29	37 "	5.9
30	38 "	5.0
31	39 "	7.0 (very fat)
32	40 "	6.0
33	40 "	6.4
34	40 "	4.9
35	40 "	5.0
36	40 "	6.4
37	42 "	5.0
38	43 "	6.3
39	43 "	4.5
40	44 "	4.9
41	44 "	5.8
42	44 "	5.5
43	45 "	5.5
44	46 "	4.9
45	48 "	4.9
46	48 "	5.3 (*Cont'd p. 228.*)

TABLE LVIII—CONT'D

MEASUREMENTS OF NEEDLE IN ADULTS

NO.	AGE	LENGTH OF NEEDLE IN CM.
47	48 years	5.5
48	52 "	5.2
49	53 "	5.1
50	53 "	10.0 (very fat)
51	53 "	6.0
52	54 "	5.2
53	55 "	5.3
54	55 "	6.7
55	57 "	5.4
56	57 "	5.6
57	60 "	4.1
58	60 "	5.9
59	60 "	6.0
60	60 "	5.9
61	61 "	5.9
62	65 "	8.0

4. There may be an absence of fluid at the lower part of the spinal canal. This may be caused by a subarachnoid block as may occur in meningitis, in hydrocephalus and in cord tumor.

5. It may be due to a deformity of the vertebra such as may occur in advanced cases of tuberculosis of the spine, in rickets or spondylitis deformans.

If no fluid is obtained the stylet should be reintroduced into the needle to clear it of any particles that may be clogging the lumen, and it should then be withdrawn again. If there is still no sign of fluid the needle should be moved a little deeper or withdrawn slightly and should be rotated. If fluid is still not forthcoming, the needle should be removed and reintroduced one space higher. If after this procedure there is still no fluid an ethylchloride spray applied to the thigh may start the flow. If after repeated trials no fluid escapes, one may ascertain whether the spinal canal has been reached by the following method: The first needle is left in its original position, and a second needle is introduced one space higher. A solution of sterile salt is injected into the higher needle. If the first needle is in the

canal, the salt solution will flow out of it. When this happens it indicates that in all probability no fluid can be obtained because the canal is dry. As a rule one should be careful about pronouncing a puncture dry. A failure to obtain fluid may nearly always be attributed to some fault in the technic.

If the case shows symptoms of meningitis in spite of the fact that no fluid can be obtained by the spinal route, a ventricular or cistern puncture should be done. The technic of these punctures will be described later.

The Presence of Blood in the Fluid

The presence of blood may be due to intracranial hemorrhage or to piercing of some vein of the plexus in the spinal canal. If the presence of blood in the fluid is due to the striking of the plexus of veins, the exuding fluid has the color of fresh, venous blood and becomes progressively clearer as the cerebrospinal fluid flows out. If it is due to cerebral hemorrhage, the blood in the fluid is dark red, and if the hemorrhage is one of long standing, clotted particles of blood may be seen clinging to the needle or coming out of the lumen. Moreover, successive portions of the cerebrospinal fluid are equally bloodstained. If traumatic blood is present in the fluid and clear fluid is imperative for diagnosis, it may frequently be necessary to wait three days before repeating the puncture for it usually takes this length of time for all traces of blood to leave the cerebrospinal fluid.

Collection of the Fluid

Some physicians collect cerebrospinal fluid in graduated medicine glasses, so as to be able to measure the exact amount. This method of collection, however, is not advisable as it is hard to keep the fluid sterile in a wide glass, and it is also hard to observe the characteristic sediment in cases of meningitis. It is therefore best to collect the cerebrospinal fluid in test tubes.

The test tubes in which the fluid is to be collected should be sterile and chemically clean. It is best to use tubes of uniform size, Wassermann tubes being preferred to larger tubes. The glass of the tube should not be too thick as this may cause the fluid to have a green or yellow tint, and its opening should be stoppered with a cotton plug, unless special tests requiring a slow escape of CO_2 are to be made.

It is unwise to collect all the fluid into one test tube, as the tube may accidentally be broken and all the fluid will be lost. It may also happen that the fluid which is clear at first may become bloody later, if the needle punctures the plexus of veins due to the movements of the patient. It is therefore best to collect the fluid into more than one test tube. For the sake of uniformity, the following method has been found useful:

Into the first test tube, two c.c. of cerebrospinal fluid is collected. This amount is used for making a culture if an acute infectious process of the central nervous system is suspected. Some of this fluid may also be used for a direct smear for microscopic examination of cells and organisms. If no culture media are at hand, and a culture is desired, this tube should be kept sterile and placed in the incubator until such time as the media can be obtained. If no culture is desired, the entire contents of the first tube may be used for direct smears, to determine the type of cells in the fluid.

In the second test tube, 3 to 5 c.c. of fluid is collected. If the pressure is not increased the contents of this test tube should be used for the globulin tests, cell count, Wassermann and Lange. If the pressure is increased and an infectious process of the meninges is suspected, this test tube should be put into a tube rack for the formation of a pellicle. Care should be taken that the fluid is not disturbed.

If there is a large amount of fluid present, a third and fourth tube should be taken. Into the third tube should

be run from 5 to 8 c.c. of fluid. This fluid should be used for chemical and immunologic examination.

Into the fourth tube should be run all the rest of the fluid desired for collection.

In normal cases where the pressure is not increased only 5 to 10 c.c. of fluid should be withdrawn. In all cases of increased pressure a greater quantity of fluid should be removed. In delirium tremens, 10 c.c. usually suffices to quiet the patient. In meningitis, 25 to 40 c.c. may be withdrawn on account of the greatly increased amount of fluid in the canal. Even in severe cases of meningitis, however, it is not advisable to remove more than 40 c.c. at one sitting on account of the danger of inducing shock. The quality of the pulse is a good guide as to the amount of fluid to remove.

VENTRICULAR PUNCTURE

Ventricular puncture is indicated:

1. When a contraindication to lumbar puncture exists.

2. When no fluid can be obtained by lumbar puncture either because of a deformity or anomaly of the spine.

3. If repeated lumbar punctures result in dry or bloody taps, and fluid must be obtained for diagnosis.

4. For the diagnosis of conditions affecting the ventricles and their apertures; e.g., obstructive hydrocephalus. Cushing has called attention to the fact that meningococci may be found occasionally in the ventricular fluid in cases of postmeningitic obstructive hydrocephalus, long after the organism has disappeared from the lumbar fluid.

5. For the injection of air for ventriculography in the diagnosis of hydrocephalus or brain tumors.

6. For the injection of serum, especially meningococcic, in the acute stages of purulent meningitis; also in obstructive hydrocephalus resulting from meningitis.

7. For combined puncture the diagnosis of subarachnoid block.

In infants before the closure of the anterior fontanelle, ventricular puncture is a relatively simple procedure and is to be preferred to cistern puncture, when either method will do. In adults, however, ventricular puncture is a greater operative risk than cistern puncture and should be used only if no other route is available.

Fig. 52.—Photograph showing ventricular puncture in infant by way of the anterior fontanelle. Dark circular spot shows needle in position. (Front view.)

The contraindications to ventricular puncture are mainly local, such as infections of the scalp, or deformities of the skull which increase the risk of infection.

The technic employed for a ventricular puncture in in-

fants when the anterior fontanelle is not yet closed, is as follows:

The patient is wrapped in a sheet and placed in the supine position with the head close to the edge of the table. The region of the anterior fontanelle is shaved, washed with alcohol and ether, and painted with iodine. The needle to be used should be sterilized and all other necessary aseptic

Fig. 53.—Photograph showing ventricular puncture in infant. (Side view.)

precautions should be taken. A short spinal puncture needle or an ordinary Luer needle may be used. When a spinal needle is used, the stylet should be left in the needle the same as in lumbar puncture. The head is held firmly by an assistant; and the needle is introduced into the anterior fontanelle. Any part of the fontanelle will answer the purpose, but it is best to introduce it ½ to 1 cm. to one side of

the median line to avoid the sagittal sinus. (Figs. 52 and 53.) The needle should be directed forward and outward. In normal infants the needle should be introduced 1 to 1⅔ inches in depth. In marked hydrocephalic infants it is necessary to introduce the needle only ¼ to ½ inch. After the desired amount of fluid is obtained, the needle is removed and collodion applied to the punctured surface. In infants with marked hydrocephalus where the frontoparie-

Fig. 54.—Photograph showing ventricular puncture in infant by way of the left fronto-parietal suture. The white area in the center shows the bulging anterior fontanelle.

tal suture is wide open, the ventricle may be tapped through this suture (Fig. 54).

If a ventricular puncture does not yield sufficient fluid for all determinations desired, the needle may be withdrawn and reinserted on the opposite side of the fontanelle into the opposite ventricle.

In adults, ventricular puncture is done either for therapeutic purposes, especially for the relief of intracranial

pressure or for the diagnostic procedures of ventriculography or combined puncture. It necessitates the use of a bore or a trephine to get through the skull. The method used is that of Kocher, consisting of a trephine opening made 2.5 cm. from the median line and 3 cm. anterior to the coronal or fronto-parietal suture. The needle is then passed inward and slightly backward for a distance of 4 or 5 cm. when the lateral ventricle is reached. Since the cerebrospinal fluid pressure in the ventricles may be low or zero, the fluid may flow out very slowly or not at all. In these cases a syringe may be used for aspirating the fluid. The operation, in general, is a rather complicated one and calls for precision and careful surgical technic. It should therefore be used only when absolutely necessary and when fluid can neither be obtained nor introduced by way of lumbar or cistern puncture. As in spinal puncture so also in ventricular puncture one may obtain bloody fluid. This is usually due to the piercing of a superficial vein in the scalp. Bloody ventricular fluid is not so common, however, as bloody spinal fluid. If bloody fluid has been obtained, the ventricular puncture should not be repeated for several days.

Transitory effects following ventricular puncture include: rise in temperature, twitching, dyspnea, and oozing of cerebrospinal fluid. Occasionally the anterior fontanelle which became depressed immediately after a ventricular puncture becomes tense again in a few hours. The bulging usually disappears, however, within twenty-four hours.

CISTERN PUNCTURE

The cisterna magna contains more cerebrospinal fluid than any other portion of the subarachnoid space. In laboratory animals this fact has been made use of for the purpose of removing cerebrospinal fluid. Quincke mentioned this method in connection with human beings, but considered it dangerous, because of the proximity of the

cistern to the vital centers. Recently, however, the technic has been improved to the point that it can safely be used in human beings. No one should, however, undertake a cistern puncture unless he has practiced the procedure on cadavers.

Indications

Cistern puncture is indicated:

1. When lumbar puncture is contraindicated or when it has repeatedly failed and fluid must be obtained for diagnosis.

2. In combination with lumbar puncture for the diagnosis of subarachnoid block. This is especially valuable in the localization of cord tumors.

3. For the injection of lipiodol or air as roentgenographic contrast media in the diagnosis of lesions of the cord or cerebellar fossa.

4. Therapeutically for the relief of intracranial pressure.

5. For irrigation of the subarachnoid space in purulent meningitides.

6. For the injection of specific sera in the purulent meningitides, and of arsphenamized or tryparsamidized serum for syphilis.

The contraindications to cistern puncture are the presence of a subtentorial brain tumor, and the local contraindications of inflammation or deformities enhancing the danger of infection or injury to the medulla.

Technic

The technic of cistern puncture is as follows: The needle is introduced into the depression immediately below the external occipital protuberance. This depression can usually be palpated through the skin. A line drawn through the glabella and the upper edges of the external auditory meati passes through this depression. The needle is introduced forward, and is then directed slightly downward to

avoid the resistance of the lower occipital crest (Fig. 55). After the downward curve is made and the crest avoided, the needle is again directed forward and slightly upward until the resistance caused by the atlanto-occipital ligament and dura is broken through. The stylet is then removed and the fluid permitted to flow out.

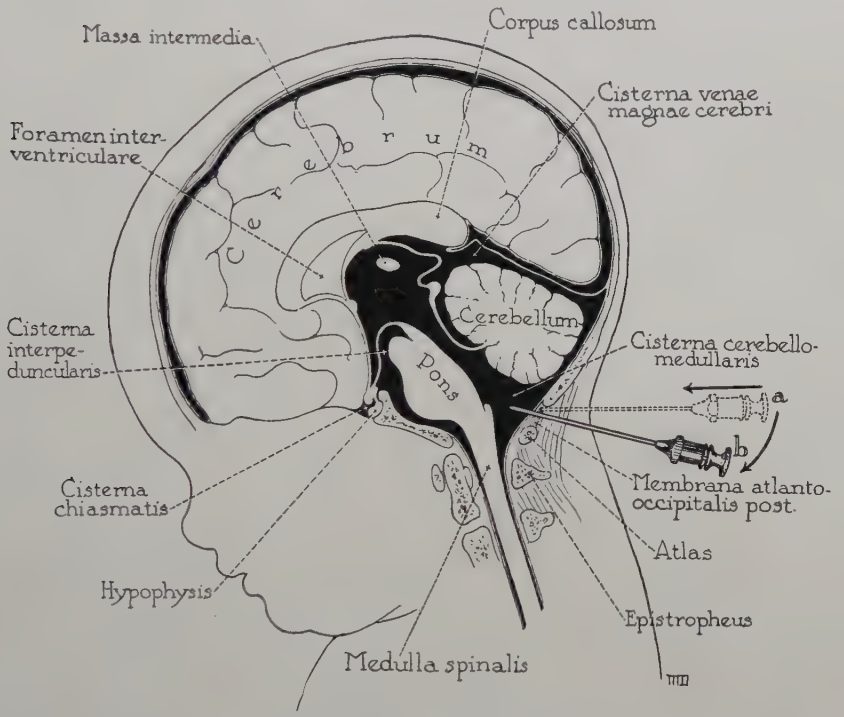

Fig. 55.—Median section of brain and coverings, showing needle in cisterna.

The collection of the fluid, of course, is the same as in spinal or ventricular puncture.

Failure and Untoward Effects

The transitory effects following cistern puncture include cyanosis, dyspnea and apnea, edema at site of puncture, and bleeding from the puncture wound. Death, due to injury of the medulla, has been reported, although I

have never encountered such a case. Hemorrhage into the cistern due to trauma following the puncture, is not an uncommon occurrence. In necropsy specimens we have frequently noted small hemorrhages in the cistern in cases that had had cistern punctures performed on them during life. Often these hemorrhages were too small to cause clinical symptoms. Presumably, a Claude Bernard's piqure may follow cistern puncture due to medullary injury, although no such case has yet been reported to my knowledge.

As a rule it is rather easy to remove cerebrospinal fluid from the cisterna magna, as the cistern is quite large and therefore contains a large amount of fluid. Occasionally, however, it is impossible to obtain fluid from the cistern because the cistern may be obliterated, as is illustrated by the following case:

M. T., five weeks old male child was admitted to the Sarah Morris Hospital on July 29, 1926, with convulsions of 24 hours' duration, followed by attacks of cyanosis occurring every two hours; there had been a foul odor to the urine for two days. The child had been born with an imperforate anus which had been operated upon the day after birth, a communicating sinus being found between the bladder and the bowel. The child recovered from the operation and the artificial anus apparently functioned well.

Physical examination showed a bulging anterior fontanelle, and nonclosure of the parietal sutures. The rest of the examination was essentially negative. The diagnosis at that time was cerebral hemorrhage, internal hydrocephalus, and congenital anomalies. Fluid obtained by ventricular puncture one month after admission was straw colored, strongly positive to Pandy, and the cell count was 47 mononuclears. Right after the puncture the child became cyanotic and had muscular twitchings and Cheyne-Stokes respiration, but later improved. Three weeks later cistern punctures were attempted twice but no fluid could be obtained. The child died on December 6th of generalized peritonitis secondary to the anomalous bowel condition. Before death an ophthalmoscopic examination showed a primary atrophy of both optic nerve heads.

At the postmortem examination the brain revealed a flattening of the convolutions. There was a very thick, firm, white area apparently of fibrous tissue over the lower surface of the cerebellum, extending to the spinal cord, and obliterating the cisterna magna. The entire white matter was very soft, the cortex was very thin and the ventricles greatly dilated.

SPECIAL METHODS

Combined Puncture

Ayer has used this method for determining the presence and location of a subarachnoid block; double lumbar puncture for cauda equina lesions, cistern-lumbar for cord and ventriculo-lumbar for cerebellar fossa lesions. If a subarachnoid block is present, the cerebrospinal fluid pressure will be higher in the needle above the site of block and lower in that below this site. Compression of the jugular will cause a rise in pressure in the former and either no rise, a smaller rise or a lagging rise in the latter, depending upon the degree of block. These punctures are done with the patient in the recumbent position.

Ventriculography

Ventriculography was first employed by Dandy in 1918 who determined the size of the ventricles in a case of hydrocephalus. Since then, it has become a valuable aid in the diagnosis and localization of brain tumors. This procedure in the best of hands carries with it a mortality of over 10 per cent and is thus to be resorted to only as a last measure. The technic consists of the injection into the ventricles of an amount of air equivalent to the amount of fluid which can be withdrawn and then radiographing the skull in four or six views to obtain an accurate conception of the size and shape of the ventricles (Fig. 56 and 57). The air is normally absorbed within a few weeks.

Myelography and Encephalography

Myelography and encephalography were first used by Dandy in 1919. The procedure consists in the injection of air or oxygen into the lumbar subarachnoid space. The gas rises and fills the subarachnoid spaces of the cord, cisterns, brain and the ventricles, which are then radiographed. This method has a limited use in the diagnosis

of tumors of the cord and brain. Its use is contraindicated in the presence of increased intracranial pressure.

Lipiodol Injections

Lipiodol injections into the subarachnoid space either through the cisterna magna or the lumbar cord were used

Fig. 56.—Ventriculogram in case of hydrocephalus.

by Sicard in 1924 as a means of localizing tumors of the cord. This substance is opaque to x-rays and is nontoxic.

The technic of lipiodol injection is as follows: A cistern puncture is performed, two c.c. of cerebrospinal fluid is removed, and then one and one-half to two c.c. of lipiodol is injected. The patient is radiographed immediately after

the injection of the lipiodol, thirty minutes later, and then two hours and twenty-four hours later. If there is no obstruction in the spinal canal, the lipiodol will gravitate to the lowest portion of the canal in anywhere between two

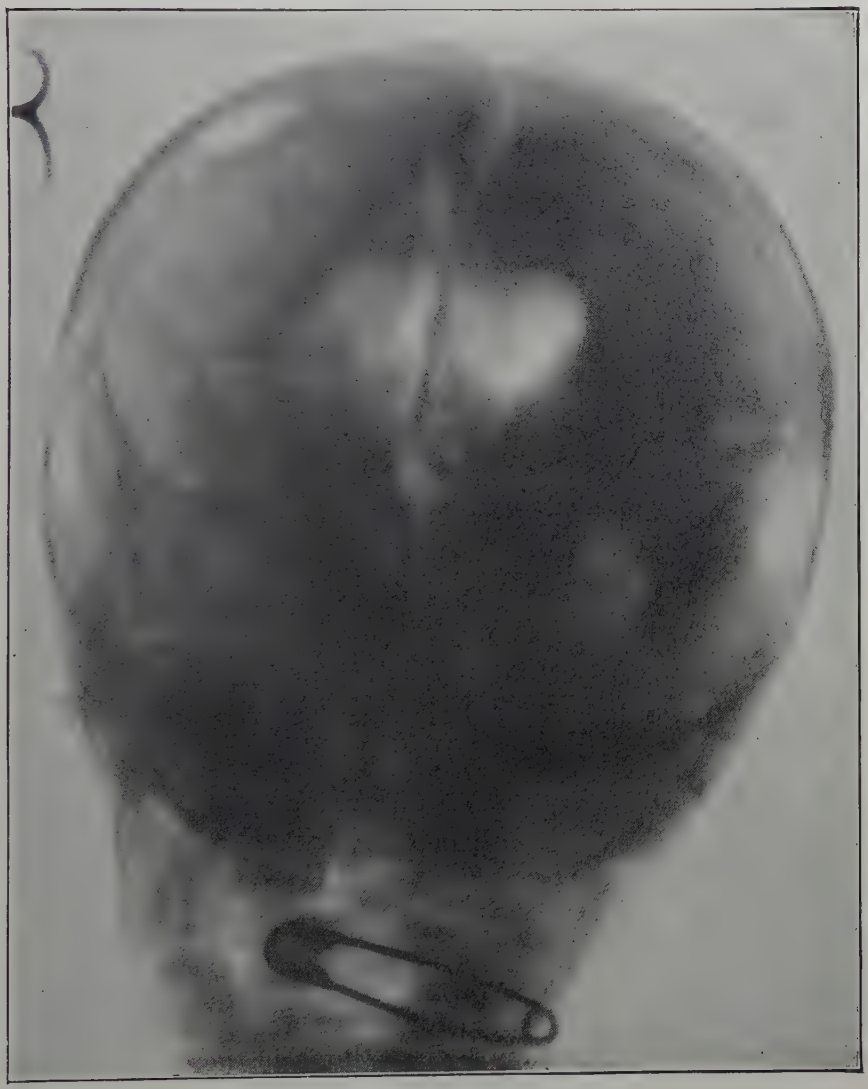

Fig. 57.—Front view of ventricles of same case.

and twenty-four hours. If there is an obstruction present, the lipiodol will be seen in the roentgenogram to settle just above the site of obstruction, and may even outline the shape of the obstructing mass. This method is to be preferred to that of myelography or encephalography. The time necessary for the absorption of the lipiodol from the subarachnoid space is unknown, but is probably several years if it is absorbed at all.

Orbital Puncture

Orbital puncture of the chiasmatic cistern was described by Bériel in 1909. Cazaman in 1916 tapped the basal cisterns by inserting a needle in front below the eye using the sphenoidal route. This method is too dangerous and the technic too difficult to master to be of any practical value. Occipito-atlantoid puncture of the cistern is to be preferred.

Epidural Injections

Epidural injection of medications in the treatment of tabes was first used by Straus in 1903. It was not until recently, however, that this method of injecting neoarsphenamine in the treatment of tabes was popularized by Hassin. The technic used by Hassin consists in introducing a spinal puncture needle through the sacral hiatus into the sacral canal which is continuous with the spinal epidural space. Through this needle 0.3 gm. of neoarsphenamine dissolved in 10 c.c. of distilled water is injected. Local anesthesia may or may not be needed. Several cases of myelomalacia following this procedure have been reported.

Sacral Anesthesia

Sacral anesthesia is used for sacral and perineal operations; e.g., prostatectomy. The technic is the same as for epidural injection except that some local anesthetic, such as novocaine or apothesine, is injected.

Spinal Anesthesia

Spinal anesthesia is being extensively used for perineal operations. The technic consists in performing a lumbar puncture, removing a small amount of cerebrospinal fluid, and then injecting the local anesthetic whether it be apothesine, novocaine, procaine or stovaine. Deaths due to bulbar paralysis following these injections have been reported.

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CHAPTER XIII

METHODS OF EXAMINATION OF CEREBROSPINAL FLUID FOR DIAGNOSTIC PURPOSES

In the following pages I shall outline the methods employed in the examination of cerebrospinal fluid for the purpose of detecting the presence of pathologic processes. I shall describe only those methods that have been proved to be both simple and practical for clinical purposes.

PHYSICAL

No special apparatus is required for the physical examination of the cerebrospinal fluid with the exception of that used for the determination of the pressure of the fluid. All other physical examinations can be made by the naked eye. The amount of fluid withdrawn can be measured either in a graduate or it may be estimated. If the amount of fluid easily withdrawn from the patient in recumbent position exceeds 10 c.c. a pathologic condition should immediately be suspected and the fluid carefully examined.

Color

The best way to examine the fluid for color is to hold it up against the light with a black background. The glass of the tube containing the fluid should be thin enough to show the color clearly and the tube itself should always be kept in the same position toward the light. Daylight naturally is better for the observation of color than artificial light. The specific changes of color in different conditions, in the various types of meningitis, and in conditions known as xanthochromia and in jaundice, are described under their respective headings.

Foam

If only five or ten c.c. of fluid is removed, the tube containing the fluid should be shaken and watched for the formation of foam. The length of time the foam persists should be observed, and its character noted, as both furnish a clew as to the presence and intensity of pathologic processes. In general, the greater the amount of foam and the longer it persists, the more likely the fluid is to be pathologic.

If more than 10 c.c. is removed, the first tube, containing 2 to 3 c.c., should be used for various examinations (cf. page 230). The second tube, containing 3 to 5 c.c., should be left undisturbed for film or pellicle formation. The third tube, containing preferably between 9 and 10 c.c., although 5 c.c. will also do, should be tested for foam formation. After the foam has subsided, the fluid in this tube may be used for any purpose desired.

Film or Pellicle

In looking for a film or pellicle, one must be careful not to disturb the fluid. It is therefore best to put the tube aside for this purpose, as soon as the fluid is collected. As for the best conditions under which a pellicle will form, no set rules can be given. Generally, a pellicle will form either at room temperature or in the cold. My experience has shown that a pellicle forms more easily at room temperature than on ice. Hence, the tube in which the pellicle is expected to form should be left at room temperature, absolutely undisturbed. The addition of one drop of blood serum to the cerebrospinal fluid will often facilitate the formation of a pellicle. Another point is that the pellicle must be examined not later than twenty-four hours after the withdrawal of the fluid, as autolysis often takes place in the pellicle on standing for two or three days. (Fig. 58.)

Pressure

The general considerations of cerebrospinal fluid pressure have been discussed in Chapter IV. For clinical work, whenever accurate cerebrospinal pressure readings are desired, it is advisable to use a spinal puncture needle with a two-way stopcock and a long hub, to which can be attached either an ordinary mercury manometer or a thin bore upright tube. An ordinary spinal puncture needle

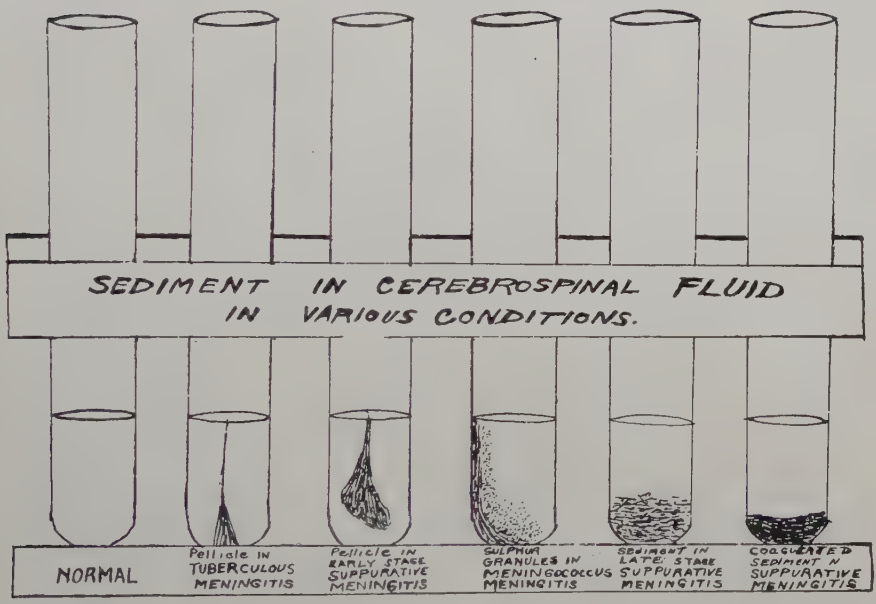

SEDIMENT IN CEREBROSPINAL FLUID IN VARIOUS CONDITIONS.
NORMAL
Pellicle in TUBERCULOUS MENINGITIS
Pellicle in EARLY STAGE SUPPURATIVE MENINGITIS
SULPHUR GRANULES IN MENINGOCOCCUS MENINGITIS
SEDIMENT IN LATE STAGE SUPPURATIVE MENINGITIS
COAGULATED SEDIMENT IN SUPPURATIVE MENINGITIS

Fig. 58.

without a stopcock, to which a manometer is attached, will also give some information as to the cerebrospinal fluid pressure, but the reading will not be so accurate as when a needle with a stopcock is used.

In most cases, one may get along without any manometer by just observing the rate of flow of the fluid. Normally, the cerebrospinal fluid flows from the spinal puncture needle at the rate of 8 to 10 drops per minute.

Queckenstedt's Sign

A lumbar puncture is done with the patient in the horizontal position, and the pressure of the cerebrospinal fluid is estimated, either by means of a manometer, or by the rate of flow of fluid from the needle. Compression is then made upon the external jugular vein, first on one side and then on the other, and the change in pressure is noted. Under normal conditions, compression of the external jugular vein causes an immediate and marked rise in intracranial and intraspinal pressure, as noted by the rise in the manometer or by the increased rate of flow of cerebrospinal fluid from the needle. In the presence of a subarachnoid block, this rise will be either delayed, lessened or absent, depending upon the degree of block. In lateral sinus thrombosis, compression of the external jugular vein on the side involved will cause either no rise, a smaller rise or a slower rise in pressure, than pressure on the unaffected side, depending upon the degree of obstruction to venous flow.

Phenolsulphonephthalein Test for Determination of Type of Hydrocephalus

Six milligrams of the dye in 1 c.c. of solution is injected into the ventricles. Simultaneously a lumbar puncture is done and fluid collected immediately, 10, 20, and 30 minutes later. If the hydrocephalus is noncommunicating, the dye will not be present in the lumbar fluid even at the end of 30 minutes. If the hydrocephalus is communicating, the phenolsulphonephthalein will be present in the lumbar fluid as indicated by the fluid turning pink upon its alkalinization with NaOH. The time it takes for the dye to appear in the lumbar fluid depends upon the degree of communication. The rate of absorption of the cerebrospinal fluid may further be estimated by determining the amount of dye excreted in the urine in a given time after its injection into the cerebral ventricles.

CHEMICAL

Many qualitative and quantitative chemical tests have been used by various scientific workers. Not all of the tests, however, are necessary or applicable for routine diagnostic purposes.

The chemical examinations of the cerebrospinal fluid for diagnostic purposes may therefore be limited to globulin tests, permanganate index, sugar, urea and chlorides. In a rapid examination of the fluid all but the globulin test may be dispensed with as the globulin increase is the one chemical factor common to all inflammatory processes, whereas the sugar and chloride content often remain unchanged. In making the chemical tests one should make sure that all the vessels employed are chemically clean.

Globulin Tests

Several globulin tests have been proposed. Among the most important of them are the Ross-Jones, Nonne-Apelt, the Pandy, Noguchi, and the sulphosalicylic-mercuric chloride tests. In doing any globulin test one must make sure at the beginning that the fluid is perfectly free of blood. Should there be over 500 red blood cells per cubic millimeter of cerebrospinal fluid, the globulin test may be positive even if no pathologic process exists. The effect of centrifugation on the fluid is not marked. I found very little difference between the globulin reaction of centrifuged and uncentrifuged specimens. A description of the various globulin tests follows:

Ross-Jones

The Ross-Jones test consists of the superimposition of 0.1 c.c. to 0.3 c.c. of a saturated solution of ammonium sulphate upon an equal amount of cerebrospinal fluid. If the globulins in the fluid are increased, an opaque ring develops at the point of contact of the fluid and ammonium

sulphate. The ammonium sulphate solution is prepared in the following manner: 85 grams of ammonium sulphate is put into 100 c.c. of water and boiled in an Erlenmeyer flask until no more salt goes into solution. This is then filtered and used for the test. The ammonium sulphate solution should be neutral in reaction, for if it has an acid reaction the results will not be accurate.

Nonne-Apelt

Phase I.—The constituents used for the Nonne-Apelt test are the same as those used for the Ross-Jones, except that equal parts of the cerebrospinal fluid and saturated am-

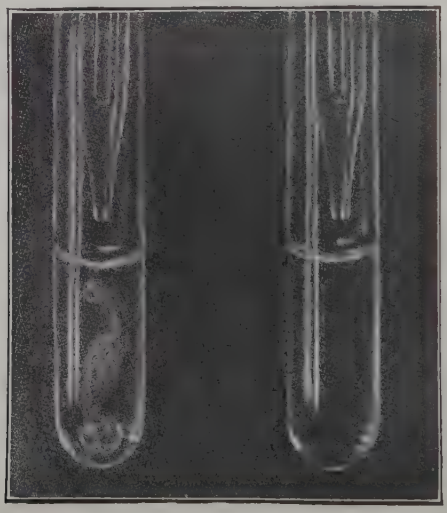


Fig. 59.—Pandy test. Left tube positive. Right tube negative. (From author's article on Cerebrospinal Fluid in Abt's System of Pediatrics.)

monium sulphate are mixed instead of being superimposed one upon the other. A white precipitation forms in three minutes if the reaction is positive (euglobulin).

Phase II.—The precipitate is filtered, one drop of 10 per cent acetic acid is now added to the filtrate and the mixture is boiled. A precipitate forms if the reaction is positive (serum albumin).

Pandy

One drop of cerebrospinal fluid is added to one c.c. of a concentrated solution of carbolic acid. A cloudy streak descending in the carbolic solution is noticed if an excess of globulin is present, the strength of the reaction being denoted by 1 plus, 2, 3, or 4 plus, depending upon the amount of precipitation. (Fig. 59.) This test is the one most widely used. The technic of the preparation of the Pandy reagent is quite important. To one part of phenol crystals are added 15 parts of water. The solution is left in the incubator for twelve hours and then filtered. The filtered solution should be crystal clear. Before it is used for testing purposes it should be controlled by a known normal and a known pathologic fluid.

Noguchi

Two-tenths c.c. of cerebrospinal fluid is transferred by means of a pipette to a small test tube, preferably a regular Noguchi tube. Five-tenths c.c. of butyric acid solution (5 c.c. of butyric acid to 45 c.c. of physiologic salt solution) is added to the fluid; this mixture is boiled for a few seconds and 0.1 c.c. of a 4 per cent aqueous NaOH solution is poured into it and it is boiled again for a few seconds. If there is an increase in the globulin of the fluid a fine or coarse granular, flocculent deposit is formed in from two to twenty minutes. If no flocculence makes its appearance within two hours, or if nothing more than a slight opalescence is present, it shows that the globulin is not increased.

Noguchi also described another test for the detection of increased protein in the cerebrospinal fluid. The reagent for the test consists of an alcoholic extract of acetone-insoluble tissue lipoids and a solution containing 0.5 c.c. of glacial acetic acid, 10 c.c. of a saturated solution of picric acid in absolute alcohol, 1.5 gm. of acid potassium phosphate and 4 gm. of sodium chlorid in distilled water to make the total volume 1,000 c.c. One c.c. of the reagent added

to 0.1 c.c. of cerebrospinal fluid shows a flocculent precipitate if the protein in the fluid is increased.

Noguchi claims great accuracy for this test. However, the necessity of preparing a stock solution of acetone-insoluble lipoids, will, I believe, hinder the test from becoming popular in clinical laboratory work.

Kaplan

Five-tenths c.c. of cerebrospinal fluid is heated and boiled twice. Then 3 drops of a 5 per cent solution of butyric acid in physiologic salt solution is added to the test tube and is followed immediately by 0.5 c.c. of a supersaturated solution of ammonium sulphate. The mixture is now set aside for 20 minutes. An excess of globulin is indicated by a thick granular precipitate.

Weichbrodt's Reaction

Three-tenths c.c. of a 1:1,000 solution of pure mercuric chloride is added to 0.7 c.c. of cerebrospinal fluid. Normal fluids cause no change. Pathologic fluids become opalescent, the degree of opalescence being arbitrarily divided into 4 degrees, as in the Pandy reaction. The weaker reactions become manifest only after the lapse of a few minutes. Eskuchen noted that with this test even normal fluids become opalescent after twenty-four hours.

Boltz Test

To 1 c.c. of fresh cerebrospinal fluid in a test tube add 0.3 c.c. acetic anhydride and shake well. Then add, drop by drop, 0.8 c.c. concentrated H_2SO_4. Shake gently and examine against a white background. A positive test consists in the formation of a lilac color, which appears immediately but which may soon disappear. The reaction is negative if the color remains clear brown, yellow, or reddish yellow. Boltz states that the test is positive in all cases of general paresis and in many cases of cerebrospinal

lues, and negative in all other conditions. Several workers have confirmed this claim while others have found positive reactions in other conditions also. In conjunction with other tests, however, this test probably is of value.

Braun-Husler Reaction

To 1 c.c. of cerebrospinal fluid add 5 c.c. of N/300 HCl, 1 drop at a time. Normally no reaction occurs. In meningitis and general paresis, a turbidity or opalescence of the fluid occurs.

Alcohol Reaction

Perlstein and I have found the following test of value: To ½ c.c. of 95 per cent alcohol add 1 drop of cerebrospinal fluid. In the presence of an increased globulin content, there forms a definite precipitate immediately, the intensity of the reaction varying with the amount of protein present. In normal cerebrospinal fluid either no reaction follows or a slight precipitate forms upon waiting 1 to 2 seconds. This test is unreliable for determining small increases in protein, but is of definite value when the increase is marked.

Takata-Ara Reaction

To 1 c.c. of cerebrospinal fluid add 1 drop of 10 per cent Na_2CO_3 solution, then 0.3 c.c. of a fresh mixture of equal parts of 0.5 per cent $HgCl_2$ solution and 0.02 per cent fuchsin solution. After shaking and centrifuging, normal cerebrospinal fluid has a blue-violet color without flocculation. In metaluetic conditions, the fluid is clear like water, with a blue-violet sediment below it. The degree of precipitate is indicated as one plus to four plus. In meningitis there is a rose color to the fluid without any precipitation.

Taccone Test

The reagent is prepared as follows: One drop of trichloracetic acid is added to each 1 c.c. of a 5 per cent solu-

tion of potassium bichromate which has been heated and filtered. This solution keeps indefinitely. The cerebrospinal fluid is superimposed upon a layer of this reagent. A deep ring test forms in a positive globulin test. By this test one can detect pathology in the cerebrospinal fluid according to Taccone.

Sulphosalicylic Acid-Mercuric Chloride Method

One c.c. of cerebrospinal fluid is introduced into each of two small tubes of uniform height and width, (about 0.3 cm. in diameter; flat bottom tubes are preferable); into one of the tubes 1 c.c. of a 3 per cent sulphosalicylic acid solution is introduced, and into the other 1 c.c. of a 1 per cent mercuric chloride solution. If the fluid is pathologic, a heavy precipitate forms in the tube containing the sulphosalicylic acid and a marked turbidity in the tube containing the mercuric chloride solution. If the fluid is normal only a slight or no turbidity appears. The tubes are then allowed to stand for twenty-four hours, after which the sediment in them is measured and compared. Under normal conditions the sediment found after 24 hours in either of the two tubes is very slight; in all suppurative meningitides, however, the height of the sediment in the sulphosalicylic tube is very heavy, often being three times the size of the sediment obtained with the mercuric chloride. In tuberculous meningitis (and rarely in other conditions) the opposite takes place, the precipitation with the mercuric chloride usually being three times as high as that obtained with sulphosalicylic acid.

Two modifications of this test have been described. Pons and Fletcher use a 6 per cent sulphosalicylic acid and a 2 per cent mercuric chloride solution. Peterman uses a 4 per cent sulphosalicylic acid and a 2 per cent mercuric chloride solution.

Relative Value of the Globulin Tests

It would be well to emphasize the fact that there is no one test for the diagnosis of pathologic conditions that can

be considered absolutely final. Furthermore, even all the tests together are at times unreliable, unless supported by additional observations. A careful worker soon learns that to make a correct diagnosis he must take into account the entire picture of the disease gained from both clinical and laboratory observations. There are so many possibilities for error in laboratory work that unless one combines the clinical with the laboratory results, he is apt to arrive at erroneous conclusions. As for the relative value of the different tests, the experience of different workers varies. As a rule the Ross-Jones, Noguchi and Pandy run parallel in the same case. The Ross-Jones and Pandy have the advantage of being odorless and requiring no boiling. The Ross-Jones test is more sensitive than the Nonne. The Pandy and Ross-Jones reagents must frequently be checked, for slight errors in the preparation of the former and in the reaction of the latter will make them unreliable. The use of alcohol as a precipitating reagent has been found useful by us. Although normal fluids may give a slight positive reaction, the reaction is not so immediate or so marked as occurs in pathologic fluids. Alcohol, 95 per cent, needs no special preparation, it is easily obtained under most conditions and gives a good idea of the presence or absence of an increased globulin. It should not supplant the Ross-Jones or Pandy tests, but should be used in conjunction with them. I also found the sulphosalicylic mercuric chloride test very helpful in the diagnosis of tuberculous meningitis. Early in the course of the disease when other tests could not be depended on for definite results this test often gave a positive reaction.

The Permanganate Test

One c.c. of cerebrospinal fluid is introduced into an Erlenmeyer flask by an accurately graduated pipette; 50 c.c. of distilled water and 10 c.c. of diluted sulphuric acid (one part sulphuric acid and three parts water) are added, and

the mixture is brought to the boiling point; 10 c.c. of a decinormal permanganate solution is then introduced into the flask and the solution is boiled for exactly ten minutes. At the end of this time 10 c.c. of decinormal oxalic acid is put into the flask, whereupon the red or yellowish-red color turns white. Titration is now carried on drop by drop from a burette containing the permanganate solution until the color of the solution in the receptacle turns red and remains so for a number of minutes. The number of cubic centimeters of permanganate required to produce the end reaction is then read off and the figure is taken as the permanganate index. In doing this, one must make certain that 10 c.c. of n/10 permanganate equals 10 c.c. of n/10 oxalic acid. It is also necessary to ascertain how much permanganate is required to oxidize the water and the H_2SO_4 and this amount should be subtracted from the number of cubic centimeters of permanganate required to oxidize the cerebrospinal fluid solution. For example, if 4 c.c. of n/10 permanganate was required for the cerebrospinal fluid and 0.5 c.c. permanganate for water and H_2SO_4, the 0.5 c.c. should be subtracted from the whole number, leaving the reduction index only 3.5.

Boveri Test

Boveri simplified the permanganate test. He uses 1 c.c. of cerebrospinal fluid and 1 c.c. of a 1 per cent permanganate solution. If the cerebrospinal fluid is normal, there is no change of color on contact of the fluid with the permanganate solution. In all pathologic fluids, a yellow ring forms at the line of contact. When the fluid and the permanganate solution come into contact, the change in color appears in a few seconds or at most in a few minutes. The quicker the reaction, the more pathologic the fluid.

Ninhydrin Reaction for Albumoses (Nobel-Kafka)

Two c.c. of cerebrospinal fluid is dialyzed against 10 c.c. of distilled water for 16 hours at 37° C. using a dialysing

membrane impervious to albumen. To the dialysate add 0.2 c.c. of 1 per cent ninhydrin, boil for one minute and allow to stand for ½ hour. In the presence of albumoses, a gray-blue, blue or violet color forms, and is evidence of a meningitic process.

Quantitative Tests for Protein

The quantitative tests for protein are based upon the principle of precipitation of the protein by various agents, and then the determination of the amount of protein present, either by the Kjeldahl method, which is the most accurate, or by comparison of the amount of precipitate with previously prepared standards. Many methods have been described. I shall describe here only one of the most practicable methods.

Method of Nissl

This method is similar to the Esbach method of determination of total protein in the urine. A conical graduated tube is used (Fig. 60). The cerebrospinal fluid is put into this tube up to mark 2 (2 c.c.) and Esbach's reagent to mark 3 (1 c.c.). The tube is centrifuged for ½ hour and the height of the sediment is marked. The tube is again centrifuged, until the sediment settles no more. The percentage of protein in the cerebrospinal fluid is then read off directly on the scale, each small division representing 0.01 c.c. or 0.1 per cent of protein.

In the absence of such a tube, a plain tube 5-6 mm. in diameter and 5-6 inches long is fastened by a rubber band or by adhesive tape to an ordinary Esbach albuminometer, so that their bottoms are on the same level. The narrow tube is then filled with cerebrospinal fluid to a level corresponding to the U on the Esbach tube, and with Esbach reagent to a level corresponding to R on the Esbach tube.

The tubes are allowed to stand for 24 hours and the amount of precipitate in the narrow tube is read off on the scale of the Esbach albuminometer, the result being in grams of protein per liter of cerebrospinal fluid.

Sugar

The qualitative determination of sugar in the cerebrospinal fluid may be of some assistance in the diagnosis of a given case. When it is reduced by 5 drops of Fehling's

Fig. 60.—Tube used for determination of protein by Nissl's method.

or Benedict's solution it excludes meningitis, as the amount of sugar in meningitic fluid is too small at most to give a reduction with qualitative methods. When no reduction takes place, it does not exclude meningitis, as many normal fluids do not contain sufficient sugar to be reduced by Fehling's or Benedict's. For accurate determination of the amount of sugar in the fluid, quantitative methods should be employed.

Several methods have been used for sugar determination, the most accurate ones being the Lewis-Benedict and the Folin-Wu methods, originally described for blood sugar. The technic of the Lewis-Benedict method is as follows: 2 c.c. of cerebrospinal fluid is put into a 25 c.c. volumetric flask containing 5 c.c. of distilled water, 15 c.c. of saturated picric acid solution is added, water filled up to 25 c.c. and the whole solution is shaken and filtered. Eight c.c. of the filtrate in duplicate are put into large Jena test tubes for determination; 2 c.c. saturated picric acid solution and 1 c.c. of a 10 per cent sodium carbonate solution are added; the contents of the tube is evaporated over the flame until precipitation occurs, 3 c.c. of water is added and the tube heated again to the boiling point, in order to dissolve the precipitate. The content of the tube is now transferred to a 10 c.c. volumetric flask, cooled, filled up to the mark with water, shaken and filtered through cotton into a colorimetric flask; the color is compared in a Duboscq colorimeter either with a dextrose standard, freshly made up every time, or with a permanent standard consisting of 0.064-mg. picramic acid and 0.1 gm. sodium carbonate in 1000 c.c., and the results are calculated.

Epstein described a rapid microchemical method for the determination of sugar in the blood which I believe may easily be applied also to the cerebrospinal fluid. The principle is the same as that of the Lewis-Benedict method, except that a permanent standard is used and smaller quantities of the fluid to be tested are used. It differs from the blood sugar test also in that in the determination of sugar in the cerebrospinal fluid, no sodium fluoride or potassium oxalate has to be used as is the case in sugar of the blood. The apparatus consists of the following:

(a) A Sahli-Gower hemoglobinometer stand and a graduated tube.

(b) Two standard color tubes, one for measuring quantities of sugar ranging from 0.05 to 0.1 per cent and the other for measuring quantities of sugar over 0.1 per cent.

(c) A test tube (½ by 4 inches) graduated at 1.0 c.c. and 2.5 c.c.

(d) A special pipette graduated at 0.1 c.c. and 0.2 c.c. (As will be seen later, this pipette may be dispensed with.)

(e) A test tube suitable for boiling fluid.

The procedure is as follows: 0.2 c.c. of cerebrospinal fluid is drawn up with the pipette of the apparatus or any other graduated pipette into the large graduated test tube. Distilled water is then drawn up into the pipette and discharged into the graduated test tube, till the fluid reaches the 1.0 c.c. mark; picric acid is added to the 2.5 c.c. mark, and the tube shaken vigorously; the contents are filtered through a small filter, or centrifuged for 2 to 3 minutes; 1 c.c. of the filtrate is now withdrawn, put into the boiling tube and heated carefully over the naked flame. The contents of the tube are boiled until all but 2 or 3 drops of the solution is evaporated. Five-tenths c.c. of a 10 per cent soda solution is now added and the tube heated again until the contents are down to a few drops, the color of the fluid being changed from yellow to deep red or reddish brown. Three or four drops of distilled water are added and the tube warmed gently. The contents are next transferred to graduated tube 1. The boiling tube is rinsed several times with a few drops of water, the tube being warmed with each rinsing. The volume of the fluid is then made up to mark 50 on the scale. The color of the resulting solution is now compared with one of the two standard tubes, A or B. If the fluid tested is darker than the standard A which represents 0.05 per cent of sugar, and is lighter than standard B which represents 0.1 per cent of sugar, the first standard is used for comparison. The solution in the graduated tube is gradually diluted with water until the

color matches. The percentage of sugar on using standard A is figured out, each reading on scale being 1/1000. For example, if the reading is 86 then 86/1000 = 0.086 per cent. If B is used, the figure on the scale is multiplied by 2 divided by 1000. For example, if the reading is 73, then

$$\frac{73 \times 2}{1000} = 0.146.$$

I have checked the Epstein method against the Duboscq colorimeter with a standard solution of dextrose. The determination by the Epstein method usually gave a higher reading of dextrose than the amount originally started with. The percentage of error, however, was small. I think it could be accounted for by the fact that the picramic acid used by Epstein in the standard tubes loses some of its potency in time; the result being that the solutions to be tested gave a higher percentage of sugar than the solution really contained. I have also encountered difficulty in using the pipette designated by Epstein for drawing up the fluid. The lumen of the pipette was too large so that when I succeeded in getting 0.2 c.c. of cerebrospinal fluid, the fluid would run out of the tube before I had a chance to empty it into the test tube. This difficulty, however, was done away with by calibrating my own tubes, using graduated pipettes and ordinary centrifuge tubes for that purpose, so that I had a double check on the amount used. I let the cerebrospinal fluid drop down into the centrifuge tube up to the 0.2 c.c. mark on the tube, using the same tube for the purpose of centrifugation.

Chlorides

For the quantitative estimation of chlorides in the cerebrospinal fluid, the Seelman method originally described for the determination of chloride in urine is the most practical. It requires only 0.5 c.c. of fluid and the results are quite accurate.

Two solutions are prepared for the test. Solution 1 consists of the following:

Anhydrous, crystallized silver nitrate, (C. P.)	29.055	gm.
25% nitric acid in distilled water	900.	c.c.
Cold saturated solution of ammonioferric alum in distilled water	50.	"
Distilled water, q. s.	1000.	"

Solution 2 consists of:

Ammonium sulphocyanate	7	gm.
Distilled water	1000	c.c.

Solution 2 is intentionally made too strong, and must be standardized by adding distilled water in such an amount that exactly the last drop of 2 c.c. of this solution will bring about the end reaction when added to 1 c.c. of Solution 1. The end reaction consists of a reddish-brown color, which does not disappear on moderate stirring. If the second last drop produces a discoloration which disappears rather slowly, and the last drop a deep brown color, the solution must be still further diluted, until the discoloration on the addition of the last drop is a light reddish-brown, which does not disappear on stirring fifteen to twenty seconds.

The test proper is made as follows: 0.5 c.c. of cerebrospinal fluid to be tested is placed in a porcelain dish; 1 c.c. of Solution 1 is then added and the mixture is stirred for about a minute with a glass rod. Solution 2 is now added drop by drop by means of a 2 c.c. pipette graduated to at least 0.05 c.c. and the mixture is stirred until the brown color developing after each drop disappears. The amount of Solution 2 which has been used to bring about the end reaction is now read off, and the difference between this and 2 is equal to the number of grams of sodium chloride per 100 c.c. of the specimen tested. If for example, it takes 1.26 c.c. of Solution 2 to bring about the end reaction, the amount of chloride in 100 c.c. of cerebrospinal fluid equals 2. – 1.26 which equals 0.74 per cent of chlorides.

The determination of urea and other nitrogenous constituents are not of clinical importance and the methods are practically the same as those used for these determinations on the blood. For the technic of these methods, reference is made to any standard book on chemistry of the blood.

PHYSICOCHEMICAL METHODS

If determined accurately, specific gravity, viscosity, surface tension and freezing point, are of some value in elucidating diagnosis of pathologic conditions. However, since accurate determinations of physicochemical constants require a great deal of care and consume a good deal of time, I do not recommend most of them for routine laboratory use. I believe, for instance, that specific gravity, to be of any value, should be determined by a pyknometer, the determination of specific gravity by the urinometer method being very inaccurate, and requiring more fluid than can be spared even in pathologic conditions. The pyknometer, however, is a delicate instrument, and consumes a great deal of time in drawing up the fluid without bubbles, in weighing the instrument, and also in keeping it at a constant temperature. It is, therefore, best to leave it out in ordinary laboratory work.

H-ion Concentration

It has been shown in Chapter V that the H-ion concentration and the alkali reserve varies in the different types of meningitis especially after the fluid stands uncorked. This makes it of some diagnostic importance. I would, therefore, advise to determine the H-ion concentration and the alkali reserve whenever a sufficient amount of cerebrospinal fluid can be spared after other more important tests have been made. The method for the H-ion concentration in routine laboratory work, I would recommend, is that of Levy-Rowntree-Marriott. This method requires

only 3 c.c. of cerebrospinal fluid and very little apparatus. The gas-chain method, although more exact, requires 7 to 8 c.c. of fluid and is highly complicated. The technic of the Levy-Rowntree-Marriott method is as follows:

Three c.c. of cerebrospinal fluid is collected directly from the lumbar puncture needle, or from another test tube into a nonsol glass tube. To this is added 0.2 c.c. of the indicator which consists of a solution of 0.01 per cent of phenolsulphonephthalein. The tube with the cerebrospinal fluid is now compared in a special stand with one of the series of sealed standards ranging from a P_H of 6.6 to a P_H of 8.6.

If sufficient fluid has been obtained, it is advisable to determine the H-ion concentration immediately after the fluid has been removed from the body and also several hours later. If no large amount of fluid can be spared, the H-ion concentration should be determined only once, immediately after the removal of the fluid from the body. It must always be kept in mind that the H-ion concentration changes on standing and the time factor must be taken into consideration in order to arrive at any conclusion.

Some authors have used a dialyzing tube for the determination of the H-ion concentration of the cerebrospinal fluid by the indicator method. I have, however, found that with the exception of severe cases of suppurative meningitis where the protein content is very high, no dialysis is necessary and that the results obtained by the indicator method correspond quite well with those obtained from the gas-chain method, especially in P_H readings of 7.0 to 8.1.

For the determination of the alkali reserve, the Van Slyke method is the most accurate and requires the least amount of fluid.

Lange Gold Chloride Test

The Lange test is very sensitive and is quite helpful in detecting various forms of syphilis of the nervous system

and often also in differentiating the type of meningitis. The test, however, calls for extraordinary care and precision on the part of the one who is making it. To begin with, the vessels in which the solutions are used must be perfectly clean. Secondly, the vessels must be neutral in reaction. Thus, after the glassware has been cleaned with bichromate solution, for instance, sufficient water should be run through the vessels to make the reaction neutral. The water used in making up this solution should be doubly distilled, and if possible, trebly distilled. It is preferable to use the formaldehyde from a one-pound container than from the usual fifty-pound carboy, as the formaldehyde in the smaller receptacle does not deteriorate so rapidly nor increase its acidity so greatly. The pipettes used for measuring the cerebrospinal fluid and sodium chloride solution must be accurately graduated. Great care must also be taken not to blow the pipette in emptying the solution, for the introduction of saliva or carbon dioxide into the solution will greatly interfere with this delicate physicochemical reaction. Even after all precautions are taken and the solution compounded with utmost care, the resulting reagent is often unsatisfactory and must be rechecked. There is one point, however, in which the Lange test requires less precaution than other tests and that is in the matter of the time intervening between the drawing of the cerebrospinal fluid and the application of the test. While in an examination for pellicle or for the cells of the cerebrospinal fluid time of standing is a great factor, the examination with colloidal gold may be made even after the cerebrospinal fluid has been standing for some time.

Preparation of Reagent.—The solution for the test is prepared in the following manner:

To 1000 c.c. of triple distilled water, which is heated slowly to 60° C., 10 c.c. of a 1 per cent gold chloride solution and 7 c.c. of a 2 per cent solution of potassium carbon-

ate (K_2CO_3) are added. The mixture is then rapidly heated to 90° C. The flame is then removed and 5 c.c. of a 1 per cent formaldehyde solution is added quickly. The solution should at once assume a ruby red color. The solution when ready for use should be transparent, should be neutral in reaction, and should be precipitated by 1.7 c.c. of a 1 per cent sodium chloride solution in one hour. The solution usually keeps indefinitely without spoiling, although it is best to keep it in a bottle wrapped in dark paper.

Several modifications of the above technic have been proposed. The most recent modification is that of Lederer, who claims that his technic always gives practically uniform solutions conforming to accepted standards. His procedure is as follows:

Five hundred c.c. of distilled water is poured into a liter Erlenmeyer flask. Five c.c. of a 1 per cent solution of gold chloride, 3.5 c.c. of 2 per cent potassium carbonate solution, 0.87 c.c. of 1 per cent oxalic acid solution and 0.2 c.c. of a 2.5 per cent solution of formalin, are added to the water. The flask is placed over a flame, the base of the flask being protected with a square of asbestos, and the solution is heated gently until swirls of water begin to rise to the surface. The flame is adjusted so that the temperature of the solution remains at this point for about 40 to 45 minutes, precaution being taken not to permit bubbling to occur. At the end of this period the solution should become dark.

When this is noted, more formalin is added drop by drop, the fluid meanwhile being gently agitated by a rotatory movement of the flask. Soon a brownish-red discoloration appears following the formalin drop. The solution becomes darker and darker, changing to a reddish color, and suddenly it takes on the typical old rose hue. The flask is then removed from the flame and allowed to cool.

The amount of formalin to be used varies from about 1.7 to 2.2 c.c. In preparing several batches of solution at

the same time, each one may require a different amount of formalin, according to Lederer.

Technic of Lange Test.—The technic of examining cerebrospinal fluid for the colloidal gold test is as follows:

A series of 10 large test tubes are put in a test tube rack and numbered. Into the first test tube 0.2 c.c. of cerebrospinal fluid is poured and to it is added 1.8 c.c. of a 0.4 per cent solution of sodium chloride. Into each of the other tubes, 1 c.c. of sodium chloride is introduced. The contents of the first tube are then thoroughly mixed and 1 c.c. of the amount is poured into the second tube. The contents of the second tube are then mixed and 1 c.c. of its solution is emptied into the third tube; and so the processes continue with all the tubes, until 1 c.c. of the solution in the ninth tube has been emptied into the tenth tube. The solution in the tenth tube is then thoroughly mixed and 1 c.c. of its contents is removed and discarded. This leaves each tube with a content of 1 c.c. and gives the following series of dilution 1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640; 1:1280; 1:2560, 1:5120. Five c.c. of the prepared colloidal gold solution is then added to each test tube and the tubes are put away and the changes taking place in them observed. Generally some change occurs in a very short time, but it is best not to attempt to judge the reaction before the lapse of an hour and it is still better to wait until the next day, for sometimes it takes 24 hours for a completion of the reaction. The tubes should be read in daylight as artificial light may cause a false interpretation of the changes.

The results of the Lange test are indicated either in the form of a curve, or in numerals; thus: 0 means no change, 1 a change to red blue, 2 a change to violet, 3 to blue, 4 to pale blue, and 5 to clear; e.g., 5555500000 means that the first five tubes or the dilutions of 1:10 to 1:160 have been entirely discolored, while the last five tubes have shown no change at all. Figs. 61 and 62 indicate the type of reaction obtained in various conditions.

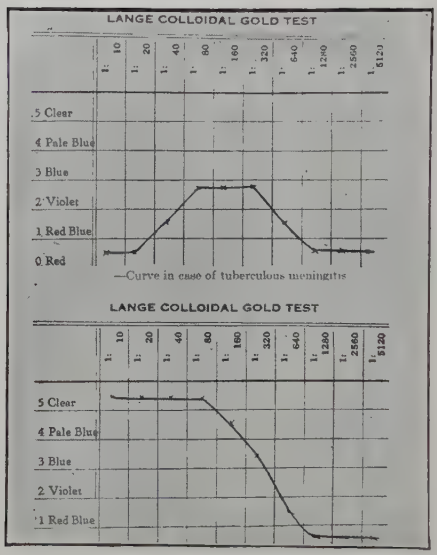


Fig. 61.—Lange curve in tuberculous meningitis (top) and in juvenile paresis (bottom). (From the author's article on Cerebrospinal Fluid in Abt's System of Pediatrics.)

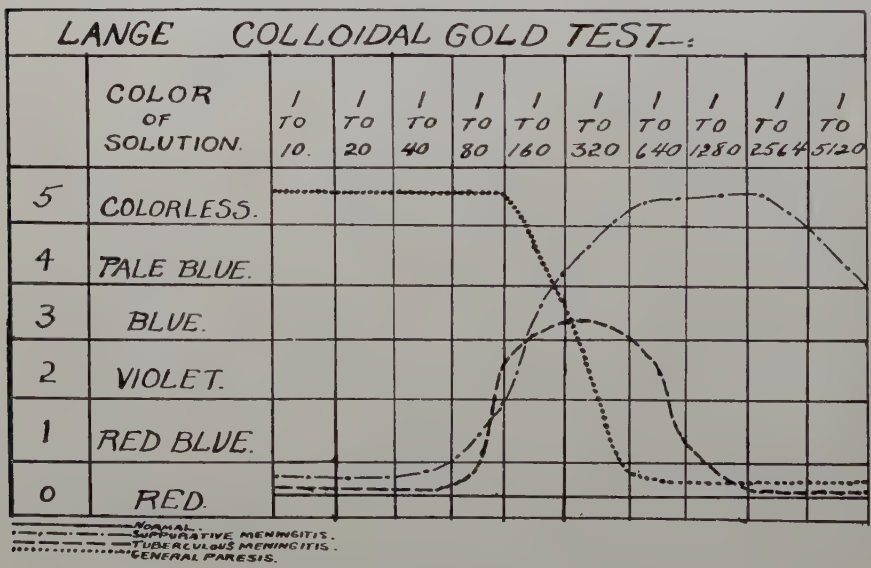


Fig. 62.—Lange colloidal gold curves in various conditions.

Mastic Test

The following technic for the Mastic test is described by Cutting:

A stock mastic solution is made by dissolving 10 gm. of gum mastic in 100 c.c. of absolute alcohol. The solution is filtered. This stock solution keeps indefinitely if well corked. To 2 c.c. of the stock solution 18 c.c. of absolute alcohol are added, and insufflated rapidly into 80 c.c. of distilled water; this makes an emulsion of mastic which is opalescent when held to the light. This solution can be used immediately or after several days. The reaction seems to be more easily read when a solution is employed which has stood for at least a few hours.

A 1.25 per cent sodium chloride solution is made with distilled water, and to each 99 c.c. of this salt solution is added 1 c.c. of a 0.5 per cent solution of potassium carbonate made up with distilled water.

The test on the cerebrospinal fluid is carried out as follows:

Six small test tubes are placed in a rack. These tubes should have been washed thoroughly in tap water, then in denatured alcohol, to remove any old mastic adhering to the sides of the tubes, rinsed in distilled water and dried, conveniently in the hot oven. To the first tube 1.5 c.c. of the combined salt and potassium carbonate solutions are added, and to the others 1 c.c. each. Then 0.50 c.c. of cerebrospinal fluid is added to the first and after thorough mixing, 1 c.c. is transferred from the first to the second, 1 c.c. from the second to the third, and so on, the last cubic centimeter that remains over from the next to the last tube being thrown out. No cerebrospinal fluid should be put in the control. One c.c. of the mastic solution is now added and stirred thoroughly with a glass rod, care being taken to wash the rod with distilled water before going to the next tube of the series.

The racks are set away, and in from twelve to twenty-four hours the end results are read. If the racks are placed in an incubator at 37.5° C., the precipitation is complete in from six to twelve hours.

Kafka and Jacobstahl found that the results were better if one worked with 12 tubes instead of 5, with dilutions of the fluid up to 1:8000 plus a control tube (tube 13). The same authors also made another modification of the original. Instead of using a 1.25 per cent NaCl solution they titrated the mastic emulsion with a NaCl solution from 0.1 per cent to 1.5 per cent. By these means they found five grades of turbidity, T_1, T_2, T_3, T_4, T_5, and three grades of sediment. They used for the test proper (with cerebrospinal fluid) the NaCl concentration that did not show any turbidity with the mastic and the one giving the first sedimentation. This gave them two curves A and B.

While the first modification, calling for the use of the larger number of tubes makes the test more valuable, the second calling for various strengths of NaCl is considered of little value by many authors.

It is claimed by Emanuel, Kafka and Jacobstahl and Eskuchen that the mastic curve varies with the type of the disease of the central nervous system. There are two main types of curves, the luetic and the meningitic. In the various forms of lues of the central nervous system, the maximum precipitation takes place in the first four tubes and also in the last three tubes, (10, 11, and 12), the precipitation in the latter group being called the negative phase.

In the various forms of meningitis, the maximum precipitation takes place in the last four tubes (dilutions 1000, 2000, 4000, 8000).

In the negative or normal fluid there is a fair degree of turbidity in the first and second tubes and very little in the third, fourth, fifth and sixth tubes.

Benzoin Test

The following technic was described by Guillain and Lechelle:

The stock solution of benzoin is made by adding 10 c.c. of absolute alcohol to each gram of the resin of benzoin (a commercial product should not be used), and then decanting the supernatant fluid. This decanted fluid if tightly stoppered will remain good indefinitely. The colloidal emulsion of benzoin which should be freshly prepared is made by adding 0.3 c.c. of this stock solution to 20 c.c. of doubly distilled water and heated to 35° C. In the original test 16 test tubes were used, but for practical purposes only five are necessary.

1st tube = 0.5 c.c. doubly distilled H_2O + 0.5 c.c. cerebrospinal fluid
2nd tube = 1.5 c.c. doubly distilled H_2O + 0.5 c.c. cerebrospinal fluid
3rd tube = 1.0 c.c. doubly distilled H_2O + 1 c.c. of 2nd tube
4th tube = 1.0 c.c. doubly distilled H_2O + 1 c.c. of 3rd tube
5th tube = 1.0 c.c. doubly distilled H_2O (control)

From the 4th tube, 1 c.c. of the mixture is then discarded. The following dilutions of cerebrospinal fluid are thus obtained: 1:2, 1:4, 1:8, 1:16, control. One c.c. of colloidal benzoin emulsion is then added to each test tube. Complete precipitation of the colloidal benzoin is designated by 5, and no precipitation by 0, with intervening degrees. Normal fluid causes precipitates in none of the tubes, the reading therefore being 0000x (x being the control tube). In general paresis reactions of the type 4433x are obtained, and in other forms of central nervous system lues 2222x are obtained. The differentiation between forms of lues of the central nervous system is not so sensitive as in the Lange test.

Relative Value of Colloidal Reactions

The Lange is beyond doubt the most valuable of the colloidal tests on cerebrospinal fluid. With properly prepared reagents the reaction can be read easily, although it happens occasionally that two samples of the same fluid will give different readings.

The mastic and benzoin tests do not always give sharp reactions nor do they always give the same result in duplicate specimens; yet, when time permits, one should apply these tests for corroborative evidence.

TESTS FOR MENINGEAL PERMEABILITY

Under pathologic conditions, many substances to which the intact meninges are normally impermeable are able to permeate the meninges. The extent to which these substances pass through into the cerebrospinal fluid may serve as an index of meningeal permeability. For this purpose, the patient is given some drug, such as sodium nitrate or sodium bromide and after a given time, the concentration of this drug in the cerebrospinal fluid is determined. Normally only traces of these substances permeate the meninges, but in the presence of a meningitis, appreciable quantities pass over into the cerebrospinal fluid. According to Cohen, the determination of the concentration in the cerebrospinal fluid of those substances normally present in the blood (such as protein, phosphates, etc.) serves as a measure of meningeal permeability without the previous administration of medicament.

Nitrate Test of Mestrezat

The patient is given one gram of pure sodium nitrate for each 30 kg. of body weight. Three hours later a spinal puncture is done and the nitrate content of the cerebrospinal fluid is estimated. Normally, the cerebrospinal fluid will contain less than 1.5 mg. of sodium nitrate per 100 c.c. In meningitis, this figure may reach 5-8 mg. per 100 c.c., the permeability being greatest usually in tuberculous meningitis. The quantitative determination of the amount of nitrate present is done as follows:

To 3 c.c. of concentrated H_2SO_4 add 3 drops of a 1 per cent solution of diphenylamine in 75 per cent H_2SO_4. To this, 3 drops of the cerebrospinal fluid are slowly added and

the blue color compared to previously prepared standards of known concentrations of nitrates by means of a colorimeter.

Uranin Test of Jervell

Jervell found that uranin (sodium fluorescin) in doses of 0.03 gm. per kg. of body weight given by mouth does not normally enter the cerebrospinal fluid. In meningitis, however, a spinal puncture done 3 hours after the oral administration of uranin, will reveal a fluid with a distinct greenish fluorescence due to the presence of the dye. In localized meningitis this greenish fluorescence will not appear.

CYTOLOGIC EXAMINATION

The examination of the cells in the cerebrospinal fluid is of extreme importance diagnostically and should be included in every routine examination of the fluid. There are essentially two methods of counting cells; one is the sedimentation, or French method, and the other is the counting chamber method.

The French Method of Cell Counting

This method, originally described by Ravaut, Sicard and Widal, is as follows: 3 to 4 c.c. of fluid is centrifuged for forty-five minutes. The fluid is then poured off and a few drops of the sediment are drawn up into a pipette of small caliber, and put on a glass slide, making a smear of uniform thickness. The slide is dried in the air, fixed in the flame, and stained with methyl blue or with Wright stain and examined under the microscope with the high power or oil immersion lens. The number in each field is now read. The results of this examination are recorded as follows:

0-3 cells per field—normal
4-6 cells per field—suspicious
7-20 cells per field—abnormal
20-150 cells per field—markedly pathologic

Chamber Method of Cell Counting

Either a special counting chamber, such as the one described by Fuchs-Rosenthal, or the ordinary blood counting chamber, such as the ones described by Thoma-Zeiss or Turk or Neubauer or the new Thoma-Metz may be used.

The Fuchs-Rosenthal chamber (Fig. 63) is larger than the ordinary leucocyte chamber, being 16 mm. square and 0.2 mm. deep, whereas the Thoma-Zeiss chamber (Fig. 64) is only 1 mm. square and 0.1 mm. deep. In order to count only the white and not the red cells a fluid which destroys the red cells is used in counting cells in the cerebrospinal fluid. A 3 per cent acetic acid solution, used for counting white

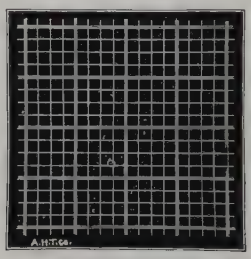


Fig. 63.—Fuchs-Rosenthal chamber for counting cells in cerebrospinal fluid.

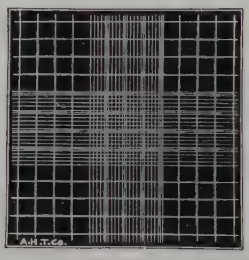


Fig. 64.—Neubauer blood counting chamber which may be used for cerebrospinal fluid.

blood cells may be used for this purpose. I found a 20% solution more useful. It is customary, however, to use a special staining fluid. This fluid consists of methyl violet 0.2 gm., glacial acetic acid 5 c.c. and water to make up 100 c.c.

In the Fuchs-Rosenthal chamber, the cells are counted in the following way: The staining fluid is drawn up into a white cell pipette to mark 1.0 and the cerebrospinal fluid is drawn up to mark 11. The cells in all the 16 squares are now counted. Since the chamber has an area of 16 sq. mm. and a depth of 0.2 mm., the result gives the number of cells contained in 16 x 0.2 mm. or 3.2 cu. mm. of diluted cerebrospinal fluid. In order to get the number of cells in 1 cu.

mm., the number of cells obtained in the field should now be divided by 3.2. However, since the fluid counted was not all cerebrospinal fluid, and since the concentration of the fluid was 10:11 (10 of cerebrospinal fluid to 11 of the volume) an allowance must be made by multiplying by $\frac{11}{10}$.

In order to get quickly the number of cells contained in 1 c.mm. of undiluted cerebrospinal fluid, the number of cells found in the 16 squares of the chamber should be multiplied by 11 and divided by 32.

In using an ordinary blood counting chamber for counting cells in cerebrospinal fluid, either 3 per cent of acetic acid or the same solution used for staining the cells in the Fuchs-Rosenthal chamber is employed. The staining fluid is drawn up into the pipette to mark 1.0 and the cerebrospinal fluid to mark 11, and the whole ruled surface of the chamber is counted. Since the ruled surface of the blood-counting chamber has an area of 9 sq. mm. and the depth of the chamber is 1/10 mm., the total count of the ruled surface will be the amount contained in the entire volume which is 9/10 cu. mm. To obtain the number of cells in one cubic millimeter of diluted fluid, this count should be multiplied by 10/9. Since to 10 parts of the cerebrospinal fluid, one part of counting fluid was added, this result corresponds to 10/11 of the number of cells in 1 cu. mm. of pure cerebrospinal fluid. Therefore, in order to obtain the number of cells in 1 cu. mm. of pure cerebrospinal fluid, we have to multiply the latter result by 11/10.

For quick calculation the number of cells obtained by counting the whole field of the counting chamber (9 sq. mm.) is multiplied by 11 and divided by 9.

Another quick method is to rinse the pipette in glacial acetic acid several times; then draw up the undiluted cerebrospinal fluid into the wet pipette and count the cells by means of a counting chamber. The small amount of glacial

acetic acid adhering to the pipette is usually sufficient to destroy all the erythrocytes in the fluid. No correction need be made for dilution.

Comparative Value of the Two Methods

The centrifuge method of counting the number of cells in the fluid is open to several rather serious objections. First of all the method is not accurate enough as it is not always easy to measure the exact amount of fluid put into the centrifuge tube. Moreover, the size of the drop taken from the sediment of the fluid cannot possibly be the same at all times. Furthermore, the force of centrifugation and the rate of velocity of the centrifuge are important determining factors. Still another drawback is the fact that the centrifuge method requires a great amount of fluid for counting, more than can usually be spared. For precise results, one should, therefore, use the counting chamber. However, when a rough estimate of the number of cells is all that is required, the centrifuge method is perhaps the more convenient one to use. Another point in its favor is the fact that it enables one to study the type of the cell on one and the same slide.

There is one thing, however, that cannot be emphasized too strongly and that is, that whatever method is employed, the examiner should thoroughly familiarize himself with it and should use it as a standard, so that he can easily detect even a slight increase in the cells. Another thing to remember is that the cells should be counted immediately after withdrawal of the fluid from the body, as they undergo autolysis upon standing.

If for some reason or other the cells cannot be counted immediately, the cells may be preserved by adding 3 drops of dilute acetic acid to each 5 c.c. of cerebrospinal fluid.

When the cerebrospinal fluid is blood stained, the specimen may still be utilized for cell counting, if only a rough count is desired. It is known that under normal conditions

the blood contains about one lymphocyte to three leucocytes. To obtain the number of lymphocytes, due to blood contamination, therefore, the polymorphonuclear leucocytes in the fluid should be counted and the result divided by three.

Type of Cells

In doing a differential cell count, care must be taken to count only the white and not the red cells or the débris. When the fluid is turbid as in meningococcus or in pneumococcus meningitis, a differential cell count may be made directly on the slide without centrifugation. When the fluid is clear, it is best to centrifuge it from fifteen to thirty minutes at about 1500 revolutions per minute. If the fluid contains only a very small amount of protein, some egg albumin may be rubbed on the slide to prevent the smear from being washed off. Methyl violet, carbol thionin, Wright, Jenner, Leischman and eosin hematoxylin are used by various workers to differentiate the type of cell in the fluid.

A special stain for the cells in cerebrospinal fluid was described by Pappenheim. It consists of 3 parts of a saturated aqueous solution of methyl green and 1 part of a saturated aqueous solution of pyronin. As a rule, however, no special stain is needed for the differential cell count, for methylene blue and next to it the Gram stain show the detailed structure of the cells quite well and stain the organisms at the same time. If tuberculous meningitis is suspected, the special carbol fuchsin stain should be used, as it shows the tubercle bacilli and also stains the cells well. By using the methyl violet diluting fluid mentioned above, a differential count may sometimes be made at the same time that the cell count is made, for the nuclei of the cells may be stained well enough to make differentiation easy.

No amount of time spent on a cerebrospinal fluid smear is wasted. Sometimes a careful study of the cells in the smear will be the only clue to the diagnosis of the existing condition.

BACTERIOLOGIC

One must be very careful in doing bacteriologic work on cerebrospinal fluid, for there are many technical difficulties such as improper media, insufficient length of time for the bacteria to develop, contamination of the media, dirty centrifuge tubes, dirty slides, overheating of the slide, (protein particles often look like bacteria) and faulty stains. At times, in a smear done by a novice I have found organisms that did not belong to the cerebrospinal fluid, but were introduced while in the centrifuge tube, or were on the slide which had previously been used for urine examination.

Culture Media

Several drops to 1 c.c. of cerebrospinal fluid obtained in a sterile test tube are planted on a culture medium. The kind of media to plant the fluid on depends on the type of organism looked for. Most organisms grow on plain agar. Meningococci have given some workers great difficulty in that they do not grow easily on ordinary media. I have grown meningococci successfully on ascitic dextrose agar and also sheep blood agar. It is strongly advisable to implant every specimen of cerebrospinal fluid on several media, such as blood agar, ascitic dextrose agar, brain broth and glucose agar. The culture should be examined microscopically after twenty-four hours' incubation, and also after forty-eight hours, as some organisms do not manifest their characteristics in less than forty-eight hours of incubation.

In addition to the culture media, it is a good plan to put some of the cerebrospinal fluid directly into the incubator and to examine it twelve to twenty-four hours later for organisms, as it has been found that some organisms, especially the meningococci, may show up well after the fluid has been incubated for several hours.

Direct Smear

If the fluid is very thick, the smear may be taken from the uncentrifuged specimen. If the fluid is clear several cubic centimeters obtained and kept under sterile conditions are centrifuged for several minutes, the supernatant fluid is poured off and the sediment is put on a slide and stained. Where suppurative organisms are suspected it is best to stain with both methylene blue and gram stain. When using the gram stain, it is wise to counter-stain only one-half of the slide, using the other half as a control to make sure that the destaining was properly done. When tubercle bacilli are searched for, the fluid should be allowed to centrifuge at high speed for forty-five minutes to one hour and the sediment stained by the Ziehl-Neelsen method. It is advisable to examine also the pellicle formed in the tube for tubercle bacilli. Care must be taken in spreading out the pellicle on the slide so as not to curl it up. At times it is necessary to put the slide in a flat sterile dish and float the pellicle on the slide by pouring the cerebrospinal fluid carefully on it.

No one but a novice will expect to find tubercle bacilli in the fluid by a hurried microscopic examination. It usually takes hours before one can detect them. Success is usually proportionate to the diligence of the searcher.

IMMUNOLOGIC

Among the immunologic tests in routine cerebrospinal fluid examinations are agglutination tests for meningococci and pneumococci, precipitin tests of cerebrospinal fluid with antimeningococcus serum, guinea pig inoculation in tuberculous meningitis, saponin test in cerebral hemorrhage and tumor, and above all, Wassermann and Kahn tests in neurosyphilis. A neutralization test has been described for poliomyelitis.

Agglutination of Meningococci

Unless the meningococci found in the culture of a given case of meningitis are agglutinated by the antimeningococ-

cus serum used, no therapeutic effect may be obtained. It is therefore advisable to do agglutination tests in all cases of meningococcus meningitis.

Two agglutination tests have been described for the meningococcus; the macroscopic and the microscopic.

Macroscopic Method.—A polyvalent antimeningococcus serum which has been proved by appropriate tests to agglutinate established strains of meningococcus in dilutions from 1:200 to 1:2000 is used.

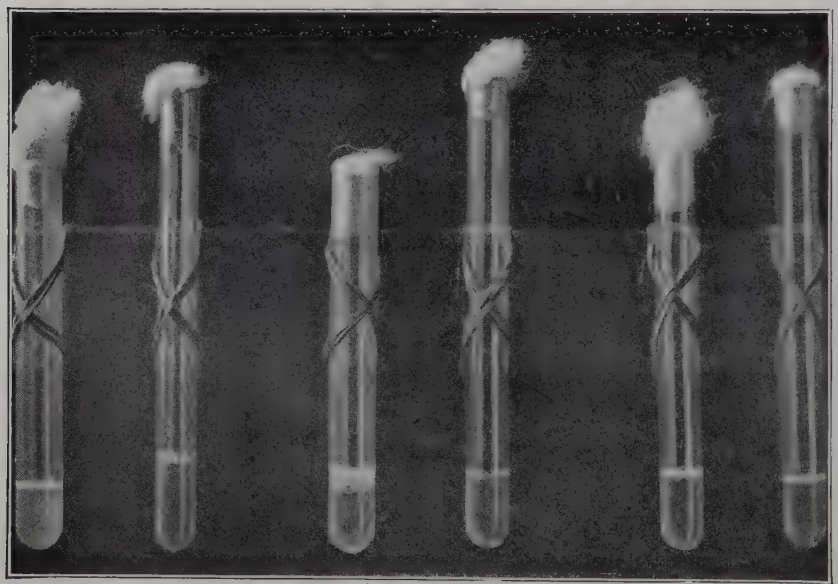
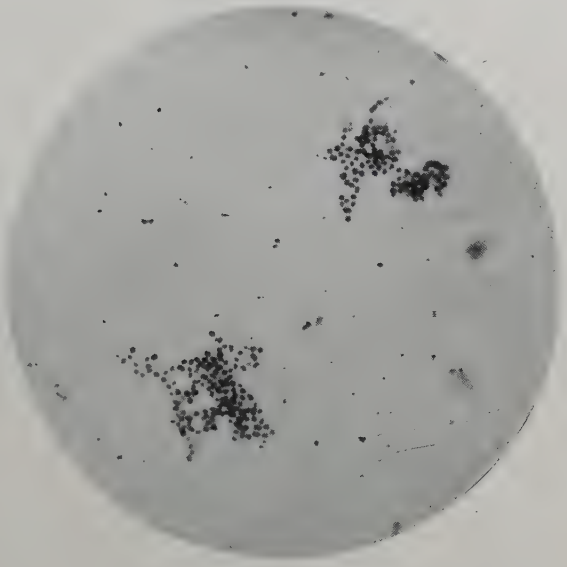


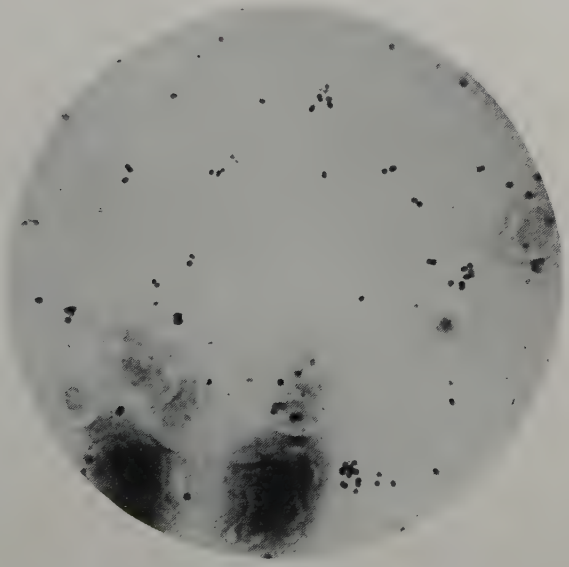
Fig. 65.—Photograph showing agglutination of meningococci by the macroscopic method.

A. Emulsion of meningococci + 1:10 dilution of antimeningococcus serum.
B. Control of emulsion of meningococci + salt solution.
C. Emulsion of meningococci + 1:160 dilution of antimeningococcus serum.
D. Control.
E. Emulsion of meningococci + 1:640 dilution of antimeningococcus serum.
F. Control.

A meningococcus culture, preferably only 24 hours old, grown on ascitic dextrose agar or on blood agar is washed down with 2 or 3 c.c. of an 0.8 per cent sterile salt solution;



A. Agglutination by specific serum.



B. Absence of agglutination with normal horse serum.

Fig. 66.—Microscopic method of agglutinating meningococci. (Tunnicliff.)

0.2 c.c. of this meningococcus emulsion is added to a series of small test tubes, each one containing 0.8 c.c. of various serum dilutions such as 1:10, 1:20, 1:40, 1:80, 1:100, 1:500, 1:1000, 1:2000 strength. This is mixed and incubated overnight (15 to 20 hours) at 56° C. Controls of meningococcus emulsion added to 0.8 c.c. of salt solution as well as controls with normal horse serum are also incubated. If the culture in question is meningococcus, a flocculent precipitate will be seen in the tubes containing the bacterial

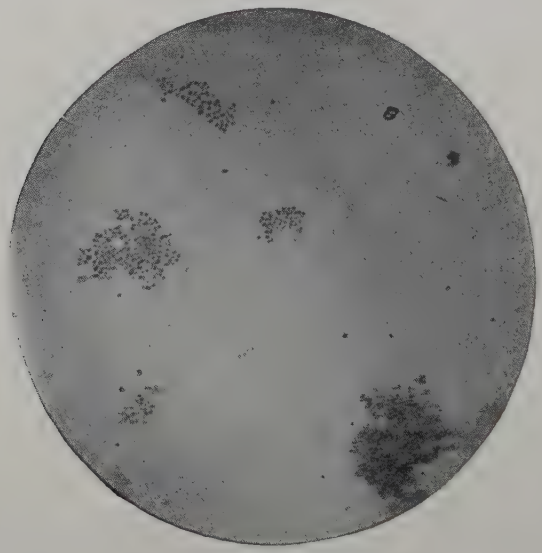


Fig. 67.—Agglutination of meningococci by the microscopic method. (Magnification 800 diameters.)

emulsion and antimeningococcus serum, the heaviness of the precipitate depending on the amount of dilution. The controls will be free from precipitate. A true meningococcus is completely agglutinated in 1:200 dilution of polyvalent serum. It is usually also agglutinated in higher dilutions (Fig. 65). The other gram-negative cocci are usually not agglutinated at all and never in greater dilutions than 1:100. Micrococcus flavus sometimes agglutinates in

polyvalent and monovalent meningococcus serum in 1:50 dilutions but may be differentiated from the meningococcus by its cultural properties.

Microscopic Method.—A more rapid method than the macroscopic for the agglutination of meningococci has been described by Tunnicliff. Equal parts of antimeningococcus serum, whole human blood in sodium citrate solution (one part of blood to 2 per cent sodium citrate in salt solution), and a suspension of organisms are incubated for ten minutes and then stained and examined. Normal horse serum with a suspension of organisms is used as control. In the mixture with normal horse serum there is very little or no clumping of the meningococcus, while in the mixture containing antimeningococcus serum there is decided agglutination (Figs. 66 and 67). The suspension of the organisms is made by adding one or two colonies of the original culture to two or three drops of salt solution. One drop of serum is drawn up in a bent capillary tube, and the upper point marked, then an equal amount of citrated blood and later the suspension of the organisms are drawn up. The content of the pipette is now carefully mixed and heated for ten minutes at 36° C., or left at room temperature for twenty minutes; after incubation the content is blown out on a glass slide, spread with cigarette paper and stained unfixed with carbol thionin or fixed with heat and stained with methylene blue.

Either of the agglutination tests gives good results. I would advise that whenever possible both the macroscopic and microscopic agglutination test should be carried out; when the time is limited the microscopic method can be depended upon.

Agglutination of pneumococci is utilized to determine the type of the organism, Type I, Type II and Type III, antipneumococcus serum being used for that purpose.

Precipitation of Cerebrospinal Fluid with Antimeningococcus Serum

According to Vincent and Ballot normal cerebrospinal fluid does not form any precipitate with antimeningococcus serum, while fluid from meningococcus meningitis is precipitated, when incubated with antimeningococcus serum.

The technic of the test is as follows: The cerebrospinal fluid is centrifuged till it becomes clear. Two to five drops of antimeningococcus serum are then added to 50 or 100 drops of the clear cerebrospinal fluid. The specimen is incubated at 50° C. for eight to fourteen hours. If the fluid is one of meningococcus meningitis, the mixture becomes turbid. A tube containing cerebrospinal fluid to which no antimeningococcus serum has been added is used as a control.

While other workers have confirmed the observation of Vincent and Ballot, it has been pointed out that at times fluids from other types of meningitis will show the same reaction with antimeningococcus serum. One of the difficulties of the test is that often it is impossible to clarify the cerebrospinal fluid of meningococcus meningitis even after centrifugating it for a long period. This test should therefore be performed only when there is sufficient fluid left over from other more necessary tests.

Guinea Pig Inoculation

It is often necessary to employ the inoculation test to decide whether or not the meningitic process is tuberculous in nature.

Five to 10 c.c. of cerebrospinal fluid is injected into the groin of a guinea pig. A month later 0.1 mg. of Old Tuberculin is injected into the axilla of the pig. If the meningitis is tuberculous in nature the pig usually dies the morning after the injection of the tuberculin. Tubercles are found postmortem in the spleen, the inguinal glands, and various other organs.

It is claimed by some authors that exposure of the guinea pig to x-ray will hasten the appearance of the tuberculous process.

Saponin Reaction

The following technic is used for testing the inhibitory power of cerebrospinal fluid on saponin hemolysis:

Nine c.c. of human blood is drawn from a vein into a flask containing a 1 per cent solution of sodium citrate. The corpuscles are now washed three times and made into a 7 per cent suspension. If human blood is unobtainable, sheep's blood will answer the purpose.

A 5 per cent solution of active saponin in distilled water prepared at intervals of one month or less, is diluted to 1 to 10,000 before the test is performed on cerebrospinal fluid. The amount of saponin necessary to hemolyze the blood corpuscles must be titrated. Hauptmann found 0.4 to 0.7 c.c. as the limit. (Table LIX.)

TABLE LIX

TITRATION

SAPONIN 1:10,000	SALT	BLOOD
0.4	0.8	0.5
0.45	0.8	0.5
0.5	0.8	0.5
0.55	0.8	0.5
etc to 0.7		

The smallest amount of saponin effecting hemolysis is taken for the test.

After the saponin unit has been determined, 0.8 c.c. of cerebrospinal fluid to be tested is set up with the required amount of saponin and 0.5 c.c. of 7 per cent sheep red corpuscle suspension. Control tubes with normal cerebrospinal fluid (one known not to produce any inhibitory affect on saponin) and with normal salt solution are also set up. The results are read after 10 minutes in the water-bath at 37°

and again after 12 hours in the refrigerator. The setting up of the saponin test with a positive result is illustrated by Table LX.

TABLE LX

				RESULT
Tube 1	1:10,000 Saponin 0.4 c.c.	Normal cerebrospinal fluid 0.8 c.c.	7% sheep corpuscle suspension, 0.5 c.c.	Complete hemolysis
Tube 2	"	Cerebrospinal fluid to be tested, 0.8 c.c.	"	Inhibition of hemolysis
Tube 3	"	0.85% saline 0.8 c.c.	"	Complete hemolysis

The Wassermann Reaction

It is impossible to describe all the details of the Wassermann reaction in a small volume on cerebrospinal fluid. I shall therefore, limit myself here to only those factors in the Wassermann reaction that have a special bearing on the subject of cerebrospinal fluid.

Different kinds of antigen are used for the Wassermann test, (a) an aqueous extract of syphilitic liver (original method); (b) an alcoholic extract of syphilitic liver; (c) an alcoholic extract of normal liver; (d) an alcoholic extract of heart (either human or beef) reinforced with cholesterin; (e) ether soluble, acetone insoluble extract of heart.

The complement consists of blood serum of healthy guinea pigs diluted with sterile normal salt solution.

The amboceptor (antisheep antibody) is contained in the serum of rabbits immunized with washed sheep corpuscles.

If the cerebrospinal fluid contains syphilitic antibodies, the antigen combines with the syphilitic antibody and the

complement, so that when antisheep amboceptor and sheep cells are added, the complement is already bound and therefore hemolysis cannot take place. If there are no syphilitic antibodies in the fluid, the complement unites with the antisheep antibody or amboceptor and the sheep

Table LXI

POSITIVE	NEGATIVE
I. Antigen + Syphilitic Antibody + Complement	I. Antigen
II. Antibody or Antisheep Amboceptor + Sheep Corpuscles	II. Complement + Antibody or Antisheep Amboceptor + Sheep Corpuscles

corpuscles and produces hemolysis. Table LXI shows the process in the Wassermann reaction of both syphilitic and nonsyphilitic cases.

The amount of fluid used for the Wassermann test is not always the same. Some use as little as 0.2 c.c. of fluid, whereas others, notably Thomson, use as much as 1.0 and even 1.2 c.c. It has been found that the small amounts do not give positive results as frequently as the larger. This fact, I believe, explains the great number of negative Wassermann reactions on cerebrospinal fluid by the older authors who used very small amounts for the tests. On the other hand, large amounts of cerebrospinal fluid such as Thomson advises are likely to be anticomplementary.

Table LXII

	TUBE 1 c.c.	TUBE 2 c.c.	TUBE 3 c.c.	TUBE 4 c.c.	TUBE 5 c.c.
Cerebrospinal Fluid	0.2	0.4	0.6	0.8	1.0
NaCl Solution	0.8	0.6	0.4	0.2	
Antigen	1.0	1.0	1.0	1.0	1.0
Complement	1.0	1.0	1.0	1.0	1.0
Amboceptor plus corpuscles	2.0	2.0	2.0	2.0	2.0

Some workers take 0.2 c.c. of cerebrospinal fluid for each of the tubes set up, varying the amount of antigen added to the tubes. As a control 0.4 c.c. of cerebrospinal fluid without antigen is used. Schottmüller advises the use of different amounts of cerebrospinal fluid in each of the test tubes as is indicated in Table LXII, a suggestion which is accepted by most workers. This gives a more or less "quantitative result" as to the degree of positiveness of the fluid.

It is best to make the Wassermann test with freshly drawn cerebrospinal fluid. If the test cannot be made immediately after the withdrawal of fluid, it should be put away in the ice box without a preservative. The cerebrospinal fluid is not inactivated. Preliminary titrations must be made on antigen, complement and amboceptor before the test is set up. The proper dose of antigen I believe to be one-fourth of anticomplementary unit and the proper dose of complement and amboceptor to be two units each. Control tubes of the cerebrospinal fluid should be set up with the test.

The cerebrospinal fluid, salt solution, antigen and complement are incubated for one hour at 37.5° C. Then the antisheep amboceptor and the sheep corpuscles are added and the solution is returned to the incubator where it is allowed to remain from 30 minutes to 2 hours. At the expiration of this time, it is taken out and examined. If hemolysis is present the test is negative; if there is an inhibition of hemolysis, the test is positive.

It should be borne in mind that a positive Wassermann reaction may become negative and remain so for several days following an alcoholic debauch. The ingestion of food has no effect on the Wassermann reaction of the cerebrospinal fluid.

Kahn Test

The Kahn test, due to its dependability and comparative simplicity, has become during recent years the standard

Table LXIII

Hospital Chart for Examination of Cerebrospinal Fluid

Date _____

Name _____

Age _____

Hospital No. _____

Diagnosis _____ _____

Method by which fluid was obtained (Spinal)_____ (Cisternal)_____ (Ventricular)_____

DATE	AMOUNT	PRESSURE		APPEARANCE	SEDIMENT OR PELLICLE	CELLS		PROTEIN				SUGAR	
		MANOMETER READING	RATE OF FLOW			NO. PER C.MM.	TYPE OF CELLS	PANDY	ROSS-JONES	OTHER METHODS	QUANTITATIVE	QUALITATIVE	QUANTITATIVE

	BACTERIA		AGGLUTINATION	ANIMAL INOCULATION	WASSERMANN	KAHN	LANGE	OTHER EXAMINATIONS	
	SMEAR	CULTURE							

method for the diagnosis of syphilis in numerous laboratories. The test does not require the hemolytic system (complement, amboceptor and red corpuscles) and can be performed in about an hour. In presenting the technic of the test for cerebrospinal fluid, only the fundamental steps will be given. For a more complete discussion, the reader is referred to Kahn's recent volume.

The test involves two basic steps: (1) The concentration of the globulins of the cerebrospinal fluid, it having been shown that the globulins carry all the syphilitic *reagen* and, (2) the carrying out of the test with the solution of concentrated globulins. Kahn recommends the use of two antigens in his test; standard antigen and sensitized antigen, the latter having been recently perfected. The outline of technic given below will be limited to the use of standard antigen. The procedure with sensitized antigen is known as the "Presumptive Procedure" and is carried out similar to that with standard antigen.

Preparation of Concentrated Globulin Solution—

Reagents.—The reagents needed for the preparation of concentrated globulin solution are: (1) cerebrospinal fluid, (2) physiologic salt solution (0.85 per cent NaCl) and, (3) a solution of saturated ammonium sulphate. This salt must be of the highest purity (Baker's Analyzed or Merck's Reagent).

Procedure.—1. Centrifuge the cerebrospinal fluid to render it free from cells and foreign particles. 2. Add 1.5 c.c. of the clear fluid to a standard Kahn test tube (7.5 x 1.0 cm.). 3. To the same tube add 1.5 c.c. of a saturated solution of ammonium sulphate. 4. Mix, covering mouth of tube with thumb (protected with rubber) shaking back and forth vigorously. Place in 56° C. water-bath for 15 minutes to hasten the precipitation of the globulins. 5. Centrifuge at high speed for about 10 minutes to completely throw down the precipitated globulins. 6. Remove with

capillary pipette the supernatant fluid as completely as possible. This is best accomplished with the aid of a finely drawn capillary pipette. The major amount of supernatant fluid is first withdrawn. The tube is then slanted at an angle of 45° and the remaining fluid is withdrawn after bringing the opening of the capillary pipette to the point of contact of the globulin precipitate and inner tube wall. It will be found that the last trace of supernatant fluid can be removed by this method. 7. Add 0.15 c.c. salt solution to the precipitate and redissolve it by gentle shaking. In adding this salt solution the pipette should be lowered close to the bottom of the tube to avoid washing down the ammonium sulphate. The globulin precipitate will readily dissolve on gentle shaking. This globulin solution is now ready to be tested with antigen suspension.

Performance of Test—

1. *Preparation of Antigen Suspension.*—(a) Measure 1 c.c. of standard Kahn antigen into an antigen suspension vial (5.5 x 1.5 cm. = flat bottom). (b) Measure an amount of physiologic salt solution indicated by the titer, into a similar vial. (c) Pour the salt solution into the antigen and, as rapidly as possible, pour the mixture back and forth six times. (d) The antigen suspension should stand 10 minutes at room temperature before its use in the test, and should be used within 30 minutes after preparation.

2. *Measuring Antigen Suspension.*—With a 0.2 c.c. pipette graduated to 0.001 c.c., measure 0.01 c.c. of the thoroughly mixed antigen suspension and deliver to the bottom of a test tube.

3. *Measuring Concentrated Globulin Solution.*—Measure 0.15 c.c. of concentrated solution into the tube containing the antigen suspension using a 0.2 c.c. pipette. Shake rack vigorously by hand for about 10 seconds to mix ingredients.

4. *Controls.*—Include positive and negative cerebrospinal fluid controls; observe each concentrated globulin solution before testing to establish that it is free from foreign particles.

5. *Shaking.*—After mixing the concentrated fluid with antigen suspension, shake the rack vigorously for 3 minutes (275 to 285 oscillations per minute).

6. *Addition of Salt Solution.*—Add 0.5 c.c. salt solution to tube and shake gently to insure thorough mixing of the ingredients.

7. *Reading of Results.*—A definite precipitate suspended in a clear medium is read four plus. Proportionately weaker precipitates are read, three, two and one plus, respectively.

Interpretation of Results.—A positive (++++, +++ or ++) reaction is indicative of neurosyphilis; a very weak (+) reaction is indicative of neurosyphilis to a lesser degree. The presumptive cerebrospinal fluid procedure is more sensitive than the regular test, and according to Kahn, is also highly specific for syphilis. The increase in sensitiveness is especially marked in treated cases of neurosyphilis, reaching as high as 20 per cent.

Peterman Microprecipitation Test

The microprecipitation test of Peterman is easily carried out, needs but little fluid, and can be done in 20 minutes. Five one-hundredths c.c. of the fluid (inactivated) is added to 0.01 c.c. of antigen and mixed in a hanging drop slide. After 10 minutes at 38° C., the mixture is examined with the low power. In the presence of syphilitic antibody, a precipitation will occur. The degree of precipitation is indicated by 1 to 4 plus.

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CHAPTER XIV

CEREBROSPINAL FLUID IN VARIOUS DISEASES

In a consideration of the cerebrospinal fluid changes in various diseases it is important to keep in mind that the changes are not stereotyped in character, but that there is a wide range of variation in the cerebrospinal fluid of one and the same disease, depending on the stage and on the severity of the disease. Yet there are many changes that are constant for a given disease. These, I shall attempt to describe in this chapter.

INFECTIOUS MENINGITIDES

Tuberculous Meningitis

The amount of fluid obtainable in tuberculous meningitis varies with the stage of the disease, being greater in the initial than in the paralytic stage. The pressure at the onset of the disease is usually very high, ranging between 300 and 700 mm. water. The pressure remains high during the irritative stage but decreases during the stage of coma. The fluid is usually clear and transparent throughout the disease, although occasionally it becomes opalescent; it shows a heavy foam on shaking. On standing from one hour to an entire day a fine pellicle forms, the pellicle being generally suspended in the center with processes projecting from its sides. There is an increase in the number of cells which range from 30 to 300 per c.mm., most of them being small lymphocytes, although early in the disease there may be a preponderance of polymorphonuclear leucocytes. The protein in the fluid is also often increased in amount. It may, however, be normal in amount. Albumose and peptone are absent, as a rule, as is also mucin.

The fluid of tuberculous meningitis also shows other variations from normal. The permanganate index is above 2 as compared with the index in nonmeningitic fluid which is below 2. The chlorides are lessened, usually running below 600 mg. per 100 c.c., sometimes falling as low as 500

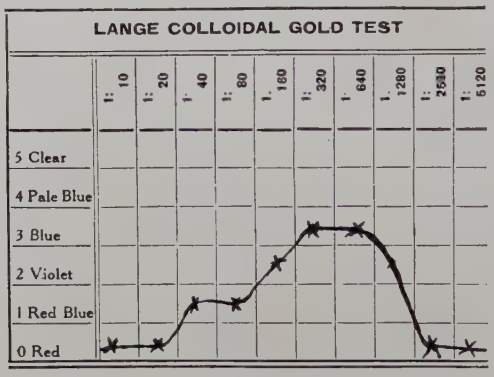

Fig. 68.—Case of tuberculous meningitis.

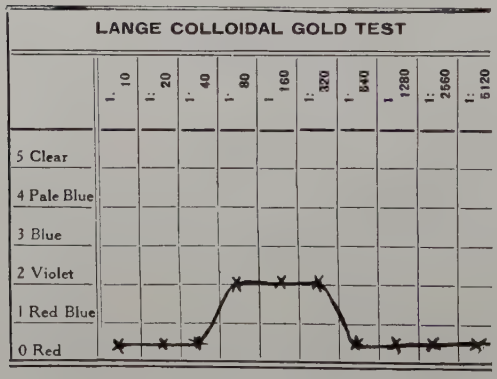

Fig. 69.—Case of tuberculous meningitis.

mg. per 100 c.c. In no other condition does the chloride content of the cerebrospinal fluid fall so low. The sugar content is usually decreased in amount averaging 14 to 30 mg. per 100 c.c. Phosphates, according to Apelt and Schumm, are present in amounts varying between 0.0034 and 0.0049 per cent.

Fig. 70.—Lange gold chloride reaction in a case of tuberculous meningitis.

The physicochemical constants also show a deviation from normal. The specific gravity, viscosity and refractometric index are increased and the freezing point raised. The P_H increases more rapidly with the age of the fluid than it does in meningococcus meningitis. The alkali reserve runs parallel with the H-ion concentration.

The gold chloride reaction varies, the reaction being 0002222000 or 0001233000. (Figs. 68, 69, and 70.) The ninhydrin test shows a discoloration with the cerebrospinal fluid.

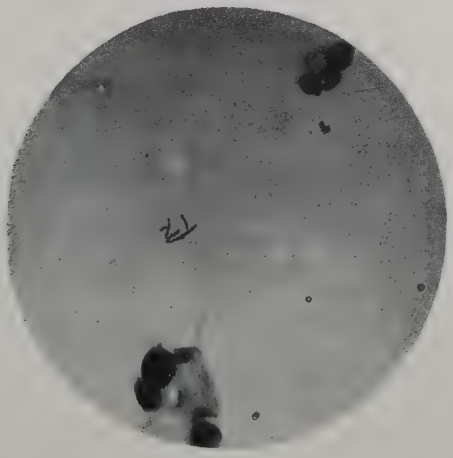

Fig. 71.—Photomicrograph showing tubercle bacilli in cerebrospinal fluid.

The cataphoresis shows most of the protein moving toward the anode. The sulphosalicylic mercuric chloride ratio is marked, the precipitate with mercuric chloride being three times as great as that with sulphosalicylic acid on standing.

Tubercle bacilli are found in the centrifuged fluid only after a careful search (Fig. 71). They are often found more easily in the pellicle. Inoculation of the cerebrospinal fluid of tuberculous meningitis into guinea pigs produces a miliary tuberculosis in the animal in course of one to six weeks.

From a diagnostic standpoint the following are the most important changes in the cerebrospinal fluid of tuberculous meningitis: Increase in amount and pressure, increase in the number of cells up to 200-300, with a relative lymphocytosis, positive Noguchi, Ross-Jones, and Nonne tests, mercuric chloride-sulphosalicylic acid ratio over 2, high permanganate index, low chlorides and sugar, Lange curve, and above all the presence of tubercle bacilli in the fluid, and the development of tubercles in guinea pigs after inoculation.

The following case will illustrate the cerebrospinal fluid changes in tuberculous meningitis:

D. H., eleven and one-half years of age, entered the hospital complaining of headache, vomiting, extreme constipation, anorexia, and weakness. The onset was slow with vomiting and headache, the vomiting being projectile in type. The patient became listless and sleepy. Examination showed marked symptoms of meningeal irritation. A spinal puncture was performed. The fluid obtained was clear and under marked pressure. The cell count showed 320 cells per cubic millimeter, 98 per cent of which were lymphocytes and 2 per cent polymorphonuclear leucocytes. The Noguchi and Ross-Jones globulin tests were strongly positive. The permanganate index was 3.0. The mercuric chloride sediment was four times the height of the sulphosalicylic sediment. The direct smear showed no organisms. The blood showed 80 per cent hemoglobin, 5,400 leucocytes per cubic millimeter, of which 58 per cent were neutrophiles, 20 per cent small mononuclear and 12 per cent large mononuclear. The Widal reaction was negative, so were the blood cultures.

The child became progressively worse and another spinal puncture was done the next day with practically the same findings as the first specimen with the additional finding of a pellicle when the fluid was allowed to stand. A third puncture showed all globulin tests to be positive, the gold chloride reaction was also characteristic of tuberculous meningitis. The patient died after staying twelve days in the hospital. The postmortem showed a grayish white, purulent exudate at the base of the brain, measuring 0.5 cm. in thickness, the exudate covering the region of the hypophysis and the right optic nerve. A part of it also extended to the right of the longitudinal fissure in the region of the parietal lobe. The exudate showed the presence of tubercle bacilli. Caseated glands were found in the hilus of the lung.

Meningococcus Meningitis

In meningococcus meningitis, the amount of the cerebrospinal fluid is increased, and as a rule, 20 to 40 c.c. can

easily be removed by one lumbar puncture. The increase in the amount of the fluid is usually a constant feature of meningococcus meningitis throughout the disease. Only very seldom does it happen that the amount of the fluid obtainable is not increased. Cases of this kind usually have an occlusion of the subarachnoid space somewhere along the tract of the cerebrospinal stem. Occasionally the exudate in the spinal canal becomes so thick that no fluid can be obtained by spinal puncture.

The pressure of the fluid in meningococcus meningitis is also increased, ranging between 300 and 700 mm. of water. In two of my cases the pressure was as high as 800 mm. of water.

The color of the fluid varies from a slight opalescence at the onset of the disease to yellowish green later in its course. The yellowish green color is the product of the meningococcus. On standing it sometimes becomes a pronounced green. The fluid remains turbid throughout the course of the disease. It occasionally happens that the fluid in the early stages of meningococcus meningitis is clear and colorless. After standing one-half hour or longer the fluid forms a sediment that changes in character with the development of the disease.

(a) In the early stages of the disease, the pellicle is made up of a yellowish-white network, the reticuli being close together forming an opaque layer. The upper portion of the network is balloon- or dome-shaped and the base or lower portion is flattened in appearance. The whole network resembles a small bursa. It usually does not reach the upper level of the fluid and generally it is seen inclining toward one side of the tube.

(b) In the more advanced stages of meningitis, the sediment formation is firmer. It generally spreads out along one side of the tube in the form of a heavy film.

(c) In still more advanced cases, a sediment of yellow granules may be seen attached to one side of the tube.

These granules are an indication that the disease has progressed to an advanced stage.

(d) In the very grave cases the sediment is thick and falls by gravity to the bottom.

When the meningitic process recedes, the pellicle or sediment becomes less marked, finally disappearing altogether.

The chemical changes in meningococcus meningitis are marked. The organic index determined by permanganate is high, ranging between 5 and 7. The protein content is greatly increased, ranging between 0.05 and 7.0 grams per 100 c.c. The Noguchi, Ross-Jones, Nonne and Pandy globulin tests are strongly positive. A 3 per cent sulphosalicylic acid solution causes a heavy sediment to form, which, on standing, measures from 10 to 20 mm. in height while a 1 per cent mercuric chloride solution gives a sediment much lower than the sulphosalicylic acid. The sugar is usually absent or greatly diminished during the active stage of the disease. Lactic acid may be present in the fluid in large quantities. The chlorides are usually diminished, but rarely fall below 600 mg. per 100 c.c., and may be normal.

Among the physicochemical changes that take place in meningococcus meningitis the following are important: Cataphoresis shows that the protein migrates to the cathode pole. The H-ion concentration is increased and it continues high for a long time after the removal of the fluid from the body. The alkali reserve is greatly lowered. The viscosity, refractometric index, and specific gravity are increased and the freezing point is raised. The gold chloride test shows changes in Tubes 6, 7, 8, 9, and 10, the reading usually being 0000035555 or 0000005554 (Fig. 72).

The cytologic changes are distinct. The leucocytes are increased in number, varying from 50 to several thousands per cubic millimeter, 90 to 98 per cent being polymorphonuclear leucocytes. The rest of the cells consists of large and small lymphocytes and endothelial cells, the latter being particularly characteristic of meningococcus menin-

Fig. 72.—Lange gold chloride reaction in a case of meningococcus meningitis.

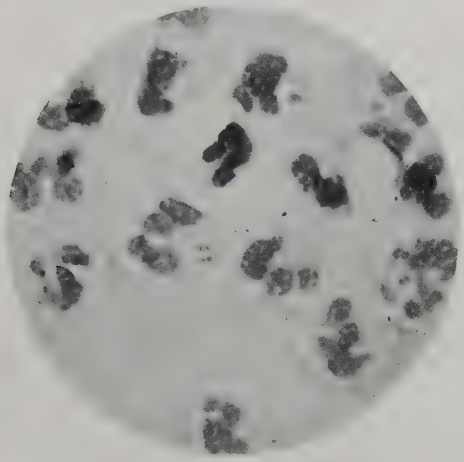

Fig. 73.—Photomicrograph showing direct smear from cerebrospinal fluid of case of meningococcus meningitis.

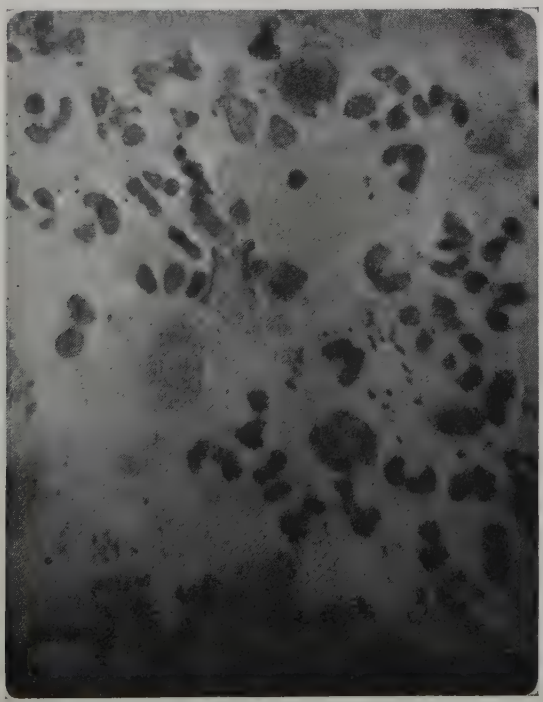

Fig. 74.—Direct smear of cerebrospinal fluid from another case of meningococcus meningitis.

gitis. One may also see many degenerating cells in the direct smear. The greater the destruction of the meninges the greater the number of degenerated cells.

The bacteriologic findings are fairly constant. A gram-negative biscuit-shaped organism is usually found in the

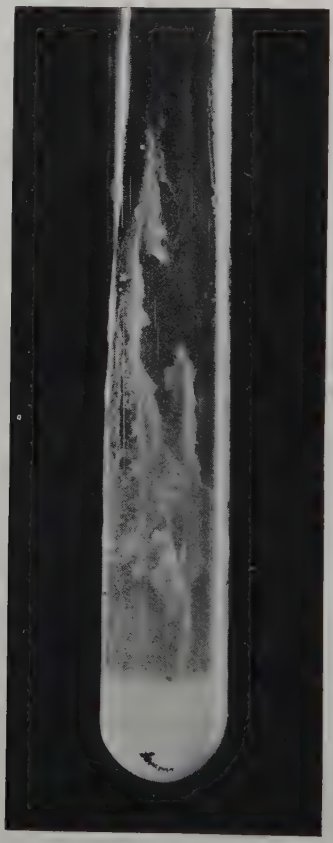

Fig. 75.—Twenty-four-hour culture of meningococci grown on ascitic dextrose agar. The culture which has been originally obtained from a case of meningococcus meningitis has been transplanted several times on artificial media, hence the heavy growth in twenty-four hours.

direct smear within the leucocytes, some being found also outside the leucocytes (Figs. 73 and 74). The number of organisms found in the direct smear varies. Sometimes there are many organisms all through the field and other

times the organisms are few. As a rule, the number of organisms in meningococcus meningitis is not nearly so great as that found in the smears from pneumococcus fluid. It sometimes happens that early in the disease the organisms in the direct smear are very scant in number, but after the first or second dose of antimeningococcus serum, there is a shower of organisms in the fluid. When the meningococci are extracellular, it speaks for a worse prognosis than when the organisms are intracellular. It happens frequently that before the injection of antimeningo-

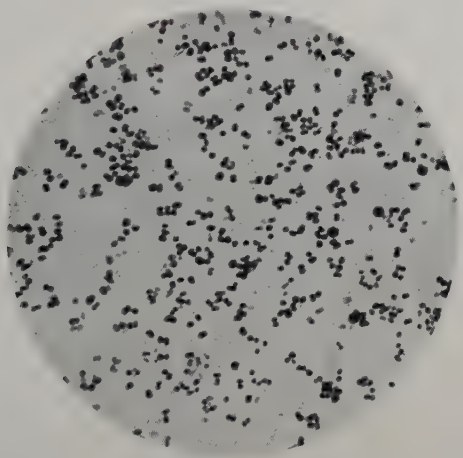

Fig. 76.—Photomicrograph of pure meningococcus culture. Twenty-four-hour growth.

coccus serum, the meningococci are mainly extra-cellular, and after the injection of one or two doses of antimeningococcus serum, the organisms become intracellular.

On ascitic dextrose agar, blood agar and brain broth, the meningococci usually grow in pure culture (Figs. 75 and 76) although it is not always easy to grow them.

The work of Dopter, Wollstein, Ellis and Gordon showed that there is more than one form of meningococcus in existence. So far, two main types and two intermediate types of meningococcus have been recognized. The diagnosis of the

type of meningococcus, however, is a matter of great difficulty.

From pneumococci, the meningococci can be differentiated by the gram stain, the meningococci being gram-negative and the pneumococci gram-positive. It is also possible to differentiate the two by the agglutination test. On the other hand, it is very difficult to differentiate the meningococci from other gram-negative cocci such as the gonococcus and micrococcus catarrhalis. However, since these organisms rarely ever produce meningitis it is seldom necessary to take them into consideration.

Occasionally it happens that a case of meningitis shows meningococci in the cerebrospinal fluid both in the direct smear and in the culture, but several days later, examination of the fluid shows both meningococci and pneumococci or pneumococci alone. Such cases have been reported by Netter and Salonier, by Mathers and by Fitzgerald. Two such cases of mixed infection also came under my observation.

One must, however, be careful in his staining technic to avoid reaching erroneous conclusions. Above all, even when the existence of a mixed infection of meningococcus and pneumococcus has been established one must not neglect giving the patient antimeningococcus serum, as this is the only hope left for him.

After several doses of antimeningococcus serum have been administered and the patient begins to show improvement, the cerebrospinal fluid gradually changes in all respects. The fluid becomes less and less turbid by degrees, the color remains yellow because of the color of the serum, but it loses its greenish tint. The amount withdrawn at each sitting is smaller than at the height of the disease; the pressure becomes lower, the protein content becomes less, the sulphosalicylic acid-mercuric chloride test approaches the normal, and the physicochemical changes grow

less and less distinct. The cells decrease in number and the type of cell changes from polymorphonuclear to lymphocytic and the bacteria disappear.

The following reports give the average changes in the cerebrospinal fluid of meningococcus meningitis:

I. M. G. Fluid cloudy, cell count 51, differential count 90 per cent polymorphonuclear leucocytes. Noguchi, Ross-Jones, and Nonne, positive. Sulphosalicylic acid gives heavy precipitate, mercuric chloride produces only turbidity. No bacteria found in direct smear.

Twenty-four hours later: Gram-negative organism on ascitic dextrose agar agglutinating in 1:200 dilution. Sulphosalicylic acid sediment measures 20 mm., mercuric chloride 5 mm., protein by modified Esbach 0.1 per cent.

Fluid examined after administration of 30 c.c. of antimeningococcus serum, —very cloudy. Cell count 218; Noguchi, Ross-Jones, and Nonne positive. Sulphosalicylic acid gives heavy precipitate, mercuric chloride only turbidity. Sugar absent. Gram-negative cocci in smear.

Twenty-four hours later: Gram-negative organisms in culture, agglutinating in 1:200 dilution, sulphosalicylic acid sediment 24 mm., mercuric chloride 6 mm., protein 0.15 per cent.

Fluid withdrawn after administration of 120 c.c. of antimeningococcus serum is yellow. Cell count 14. Differential count 50 per cent polymorphonuclears. Globulin tests slightly positive. Sugar 0.07 per cent. No organisms in direct smear or in culture.

II. E. C. Fluid turbid. Cell count 14,000; differential count 95 per cent polymorphonuclear; occasional endothelial cell. Noguchi, Ross-Jones, and Nonne positive. Sulphosalicylic acid very heavy precipitate; mercuric chloride turbid. Sugar absent. Chlorides 0.6 per cent. Permanganate index 4.0. Gram-negative intracellular diplococci.

Twenty-four hours later: No growth on ascitic dextrose agar. Protein 0.15 per cent. Sulphosalicylic acid sediment 18 mm.; mercuric chloride 6 mm.

Forty-eight-hour report: Gram-negative diplococci agglutinated by antimeningococcus serum in 1:250 dilution.

Pneumococcus Meningitis

In pneumococcus meningitis the cerebrospinal fluid is greatly increased in amount, ranging between 20 and 50 c.c. of fluid obtainable in one puncture. The color of the fluid varies according to the stage of the disease, but as a rule, it is pearly gray. On standing, a heavy sediment

forms which is usually fibrinous in character, the amount of fibrin being greater in the pneumococcic than in the meningococcic form.

In pneumococcus meningitis, the amount of protein is greatly increased ranging between 0.1 and 7.0 per cent. The globulin, sugar, chloride and physicochemical changes are the same as in meningococcic and other suppurative meningitides.

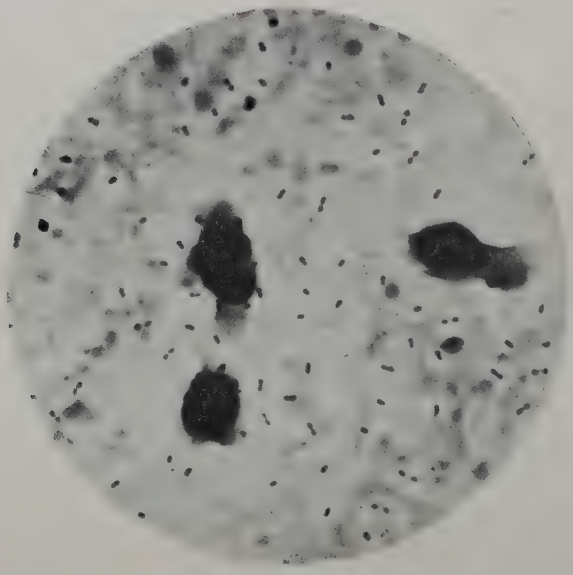

Fig. 77.—Photomicrograph of smear from cerebrospinal fluid of pneumococcus meningitis.

The cells in the fluid are increased, numbering as high as 1000 or more per c.mm. The greatest percentage of the cells are polymorphonuclear leucocytes. The pneumococci which are usually found with ease in the direct smear are present in great numbers. At times there are many gram-positive bacteria in the smear and very few cells. (Fig. 77.)

The bacteria often are arranged in chains of four or six, thus making it difficult to differentiate pneumococcus from

streptococcus. However, the fluid of pneumococcus meningitis contains a more fibrinous pellicle than does that of streptococcus. The capsule stain is also of assistance in differentiating between the two bacteria. The final diagnosis must rest on the character of the culture and on the agglutinative properties of the organism. At times, however, there is a mixed pneumococcus and streptococcus infection of the meninges.

E. B., three and one-half months old, brought to hospital with a history of fever and rigidity of neck of one week's duration. Physical examination showed, in addition to rigidity of neck, a positive Kernig sign, positive Brudzinski and twitchings of the right side of the body. The cerebrospinal fluid, removed by lumbar puncture, was increased in pressure and was very turbid. The cells numbered 1400 per cubic millimeter, of which 52 per cent were polymorphonuclear leucocytes, and 48 per cent were lymphocytes. Noguchi, Ross-Jones, and Nonne globulin tests were positive. Sulphosalicylic acid gave a heavy precipitate and mercuric chloride only a very slight one. The chlorides were 0.66 per cent. Quantitative protein by modified Esbach 0.1 per cent. The gold chloride test gave a complete discoloration in the seventh, eighth, and ninth tubes. The direct smear showed gram-positive, lanceolated organisms, arranged in pairs, which, however, did not agglutinate with either Type I, Type II, or Type III antipneumococcus serum.

The patient became progressively worse. Another lumbar puncture was made twelve hours later, but only 2 c.c. of very thick cerebrospinal fluid was obtained. A ventricular puncture was thereupon made and 25 c.c. of cerebrospinal fluid was obtained. The fluid was turbid but not as turbid as that obtained by lumbar puncture. The cells numbered 150 per cubic millimeter, the globulin tests were all positive, the chlorides read 0.74 per cent and the direct smear showed the same organism as in the first fluid.

Twenty c.c. of polyvalent antipneumococcus serum was injected into the ventricle by gravity method. The patient, however, grew constantly worse and died eighteen hours after the injection of the serum.

Streptococcus Meningitis

Hemolytic streptococci were found by me to be the most frequent type of streptococcus producing meningitis, although many cases of nonhemolytic streptococcus meningitis have also come to my attention.

The cerebrospinal fluid of all forms of streptococcus meningitis is very turbid. It is increased in amount and in pressure. The protein content is also increased and all

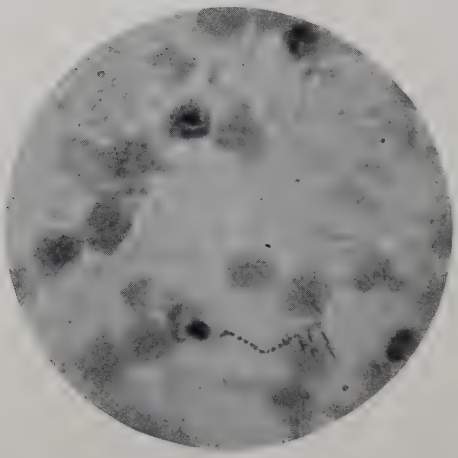

Fig. 78.—Photomicrograph showing smear from fluid of streptococcus meningitis.

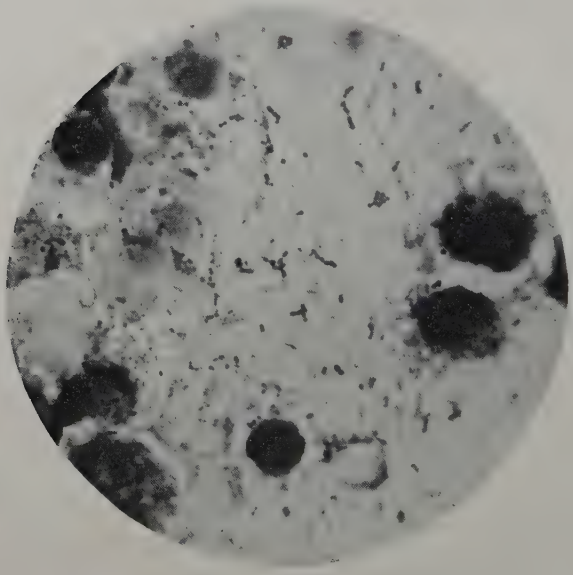

Fig. 79.—Direct smear from cerebrospinal fluid of case of meningitis due to mixed infection.

globulin tests are positive. The cells are increased and 90 to 95 per cent of them are polymorphonuclear leucocytes. The streptococci are found in the direct smear (Fig. 78) and in culture. To differentiate between the types of streptococcus, the fluid should be put on blood agar. The hemolytic streptococci will produce hemolysis.

Staphylococcus Meningitis

The cerebrospinal fluid in this condition is like that in the other forms of purulent meningitis. The pressure, globulin, and polymorphonuclear cells are increased in amount and the sugar and chlorides are decreased. The organisms appear in smears as gram-positive cocci in clusters, short chains or isolated diplococci. They may be intra- or extracellular.

Influenza Meningitis

This not infrequent form of meningitis gives an increased amount of fluid which varies in color from a slight opalescence to a distinct yellow. The cells in this condition are increased in number and range from a hundred to several thousand per c.mm. As a general rule, the cells are almost entirely polymorphonuclear, although occasionally one may find as high as 40 to 50 per cent of the cells to be lymphocytes. Gram-negative bacilli are found extracellularly in the direct smear in large numbers, the organisms often showing marked pleomorphism (Figs. 80 and 81). A special medium containing hemoglobin is required to grow the influenza bacilli.

According to Rivers, indol can be detected in cerebrospinal fluid from cases of influenza meningitis by adding Ehrlich's reagent (paradimethylamidobenzaldehyd, 4 parts; absolute alcohol, 380 parts; concentrated hydrochloric acid, 80 parts) to an ethereal extract of the cerebrospinal fluid. An old rose color at the point of contact between the two

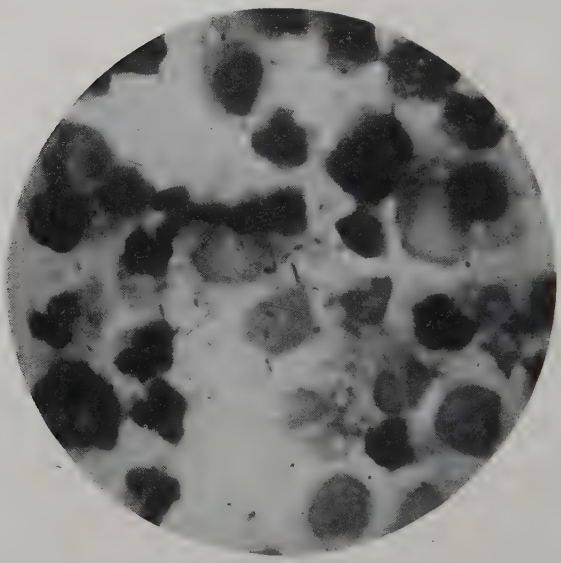

Fig. 80.—Photomicrograph showing direct smear from cerebrospinal fluid of case of influenza meningitis.

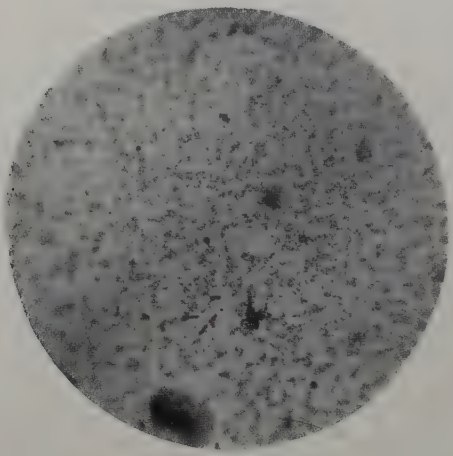

Fig. 81.—Photomicrograph of pure culture of influenza bacilli.

fluids indicates the presence of indol. This test is claimed by the author to be negative in every other form of meningitis.

Colon Meningitis

In colon meningitis the fluid is brownish or yellowish-brown in color and often has a fecal odor. There is an increase in the number of cells in the fluid, most or all of the cells being polymorphonuclear leucocytes. The colon bacillus is found both intra- and extracellularly. The culture shows short gram-negative bacilli which acidify and coagulate milk and ferment all forms of sugar.

Typhoid Meningitis

Although uncommon, typhoid meningitis is not rare, over 30 cases having been reported in the literature. The fluid in typhoid meningitis is usually increased in amount and pressure. It is turbid and may contain several thousand cells per cubic millimeter. The types of cells vary with the case. In some cases mononuclear cells predominate; in others there is a predominance of polymorphonuclear cells. The typhoid bacillus, slightly motile and gram-negative, is usually seen in the direct smear and is easily cultured. The organism agglutinates with antityphoid serum in dilutions as high as 1:3000.

Anthrax Meningitis

The cerebrospinal fluid is always bloody, and contains large numbers of anthrax bacilli.

Rare Forms of Meningitis

Gonococcus and diphtheria meningitis have been reported in the literature. These conditions are very rare, however. The fluid changes are the same as those found in other forms of suppurative meningitis. Fungi and other parasitic organisms also occasionally cause meningitis. The diagnosis in these conditions can be made upon recovering the organism from the cerebrospinal fluid and by culture.

SYPHILIS

The findings in the cerebrospinal fluid in acquired or congenital lues depend on whether or not the nervous system is involved. If there is no involvement the fluid is negative, including the Wassermann test. If there is involvement, which is quite often the case, there is an increase in the amount and pressure of the fluid, in the content of the protein, and in the number of the cells in the fluid, the cells being principally lymphocytes.

Nonne speaks of four reactions in connection with syphilis of the nervous system: positive Wassermann reaction of the blood, increased globulin, lymphocytosis and positive Wassermann reaction of the cerebrospinal fluid. Nonne's results may be summarized in Table LXIV.

Table LXIV

	WASSERMANN TEST IN BLOOD	PHASE I GLOBULIN	LYMPHOCYTOSIS	WASSERMANN TEST IN CEREBROSPINAL FLUID
General paresis	100% Positive	95-100% Positive	95%	100% positive if large quantities of fluid are used.
Tabes without paresis	60-70% Positive	85-90% Positive	90%	100% positive if large quantities of fluid are used.
Cerebrospinal lues	80-90% Positive		100%	100% positive if large quantities of fluid are used.

In addition to the reactions enumerated above, the gold chloride test in all forms of syphilis of the central nervous system, gives a positive reaction in the syphilitic zone, the reaction varying with the type of the syphilitic involvement.

In all forms of cerebrospinal lues, the permeability of the meninges to arsenic is increased. This increased permeability is probably protective in nature, as it has been shown that those cases of cerebrospinal lues in which arsenic permeates the meninges in greater quantities are the ones which react best to the treatment.

The incidence of positive Wassermann reaction in the cerebrospinal fluid of luetics as obtained by the older investigators is seen from Table LXII of Noguchi. The results of the earlier workers on this subject, however, must be discarded, for since their time, the technic of the Wassermann test has been markedly improved. It is now generally conceded that if two-tenths c.c. of cerebrospinal fluid is used, the Wassermann test is positive in 100 per cent of the cases of general paresis, in about 70 per cent of tabes, and in about 80 per cent of the cases of meningovascular lues. If one c.c. of cerebrospinal fluid is used, the Wassermann test is positive in nearly 100 per cent of all forms of syphilis of the central nervous system.

TABLE LXV

	GENERAL PARALYSIS		TABES		CEREBROSPINAL SYPHILIS	
	Number of cases	%	Number of cases	%	Number of cases	%
Marie and Levaditi	39	73	9	66.6		
Marie, Levaditi and Yamanouchi	30	93				
Stertz	45	88.8	5	60	8	0
Noguchi and Moore	60	73	11	54.5	6	50
Wassermann and Plaut	41	88				
Morgenroth and Stertz	8	100				
Plaut	54	90			4	0
Nonne	?	90	?	50	16	25
Schutze			12	66.6		
Marinesco	35	94	15	53		
Smith and Candler	64	92.1				
Noguchi, Rosanoff, and Wiseman	56	87.5				
Eskuchen		100		70		70-90

Numerous other tests for the detection and differentiation of the various types of syphilis of the central nervous system have been described. The Kahn precipitation test is more sensitive than the Wassermann test and has the same significance. The Peterman microprecipitation method is a simple and practicable method. Other tests such as the Boltz test, Takata-Ara reaction, Tar-

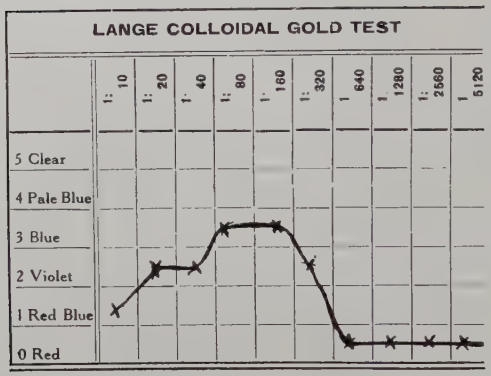

Fig. 82.—Case of cerebrospinal lues.

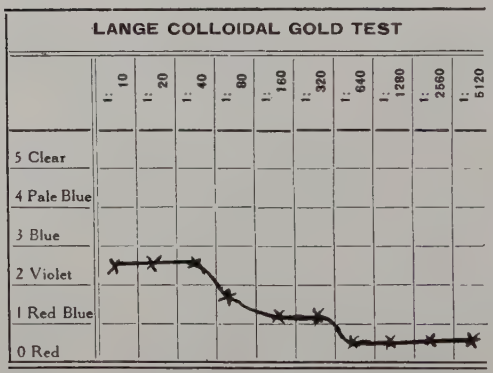

Fig. 83.—Case of tabes.

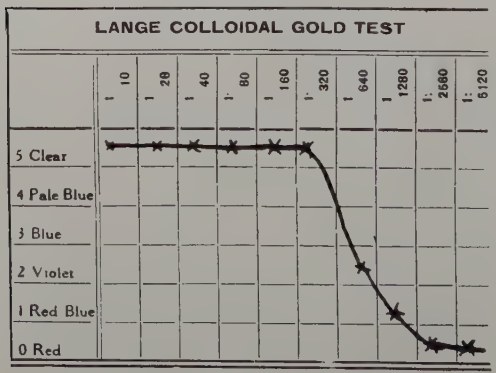

Fig. 84.—Case of general paresis.

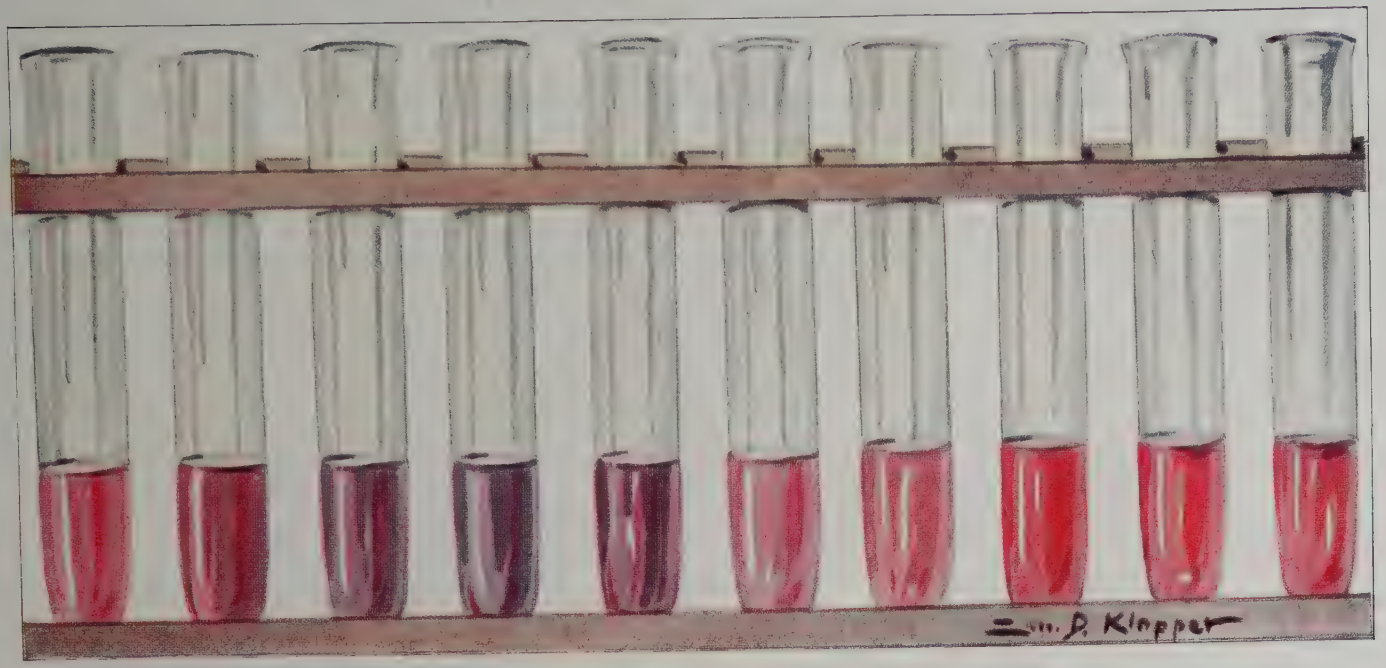

Fig. 85.—Lange gold chloride reaction in a case of tabes dorsalis.

Fig. 86.—Lange gold chloride reaction in a case of general paresis.

gowla and colloidal benzoin reactions are of limited value in the diagnosis of parasyphilitic conditions. In the early stage of syphilis, without clinical evidence of central nervous system involvement and with a cerebrospinal fluid which is otherwise normal, spirochetes may occasionally be isolated from the cerebrospinal fluid by animal inoculations.

General Paresis

In general paresis, the cerebrospinal fluid changes are rather typical. There is a moderate increase in the cerebrospinal fluid pressure. The fluid is generally clear, and the cell count is increased to 40-200 cells per c.mm., practically all of the cells being small lymphocytes. The protein is markedly increased. The character of the protein is such as to cause a discoloration in the first five tubes, and occasionally also in the seventh and eighth tubes in the Lange test (5555500000) (Figs. 84 and 86). The Wassermann test on the cerebrospinal fluid is strongly positive in 100 per cent of the cases.

Tabes Dorsalis

In this form of syphilitic involvement of the central nervous system, the changes in the cerebrospinal fluid are less marked than in general paresis. The fluid is clear and under slightly increased pressure. The cell count is 10 to 80 lymphocytes and the globulin is moderately increased. The Lange test shows a discoloration in the tubes 2, 3, 4, 5, and sometimes in 6 (0222110000) (Figs. 83 and 85). The Wassermann test on the cerebrospinal fluid is positive in over 70 per cent of the cases.

Syphilitic Meningitis

Chronic syphilitic involvement of the meninges is rather frequent, but as a rule remains unrecognized, giving few symptoms or signs. Acute syphilitic meningitis is less frequent, but it does occur occasionally and one must al-

ways keep it in mind in cases where a meningitis exists and where the exciting organisms cannot be recovered from the cerebrospinal fluid culture, and where the clinical symptoms do not justify a diagnosis of either tuberculous meningitis or acute poliomyelitis.

The cerebrospinal fluid in acute syphilitic meningitis is clear or slightly opalescent. It is moderately increased in amount, yielding generally from 15 to 25 c.c. of cerebrospinal fluid at one sitting. The fluid is moderately increased in pressure. The globulin tests are positive. The cells are greatly increased in number, running between 100 to 600 cells per cubic millimeter; 60 to 80 per cent of the cells are lymphocytes. The smears and cultures are negative to bacteria, but on careful search with the India-ink methods one may find the Spirocheta pallida. The Wassermann test of the cerebrospinal fluid is positive. The Lange test gives a reaction in the syphilitic zone, such as 2233200000. The condition may clear up on antiluetic treatment.

OTHER DISEASES OF THE CENTRAL NERVOUS SYSTEM

Tetanus

The fluid from the cases of tetanus examined by me, was negative in all respects.

Huntington's Chorea

The cerebrospinal fluid in Huntington's chorea or hereditary chorea is normal in all respects.

Epilepsy

During an epileptic attack the cerebrospinal fluid is increased both in amount and in pressure. During the intervals between attacks, both the amount and pressure of the fluid may or may not be increased. Osnato, Killian,

Garcia and Mattice found an increase in the total protein content of the cerebrospinal fluid, up to 50 mg. per 100 c.c., in epilepsy. In spite of this increase in protein, they found that the qualitative precipitation tests for protein were negative in these fluids. They therefore conclude that the cerebrospinal fluid in cases of epilepsy contains simpler tyrosine-containing compounds than protein.

These same workers also found an increase in the lactic acid content of the cerebrospinal fluid even in the interval period between attacks. This increase, however, was not great enough to change the P_H of the cerebrospinal fluid. Immediately following the epileptic seizure there is usually a rise in cerebrospinal fluid sugar. In epilepsy due to syphilis of the central nervous system, the cells and globulin content are increased and the Wassermann reaction is positive; in idiopathic epilepsy, the cells, the globulin content and the Wassermann reaction are normal. According to Donath, cholin is present in the cerebrospinal fluid of epileptics.

Rabies

The fluid is normal.

Herpes Zoster

The cerebrospinal fluid may be negative or there may be a slight increase in globulin and cells. If the latter occurs, the cell count does not return to normal for a long time after the herpetic lesions have disappeared.

Postdiphtheritic Paralysis

The cerebrospinal fluid from fifteen cases of postdiphtheritic paralysis was studied by Regan and Guinness in regard to its macroscopic appearance, cell count, protein, sugar, chloride and acetone content, permanganate index, meningeal permeability to nitrate, and colloidal benzoin reaction. The summarized results of these analyses follows:

The cerebrospinal fluid in postdiphtheritic paralysis is clear, limpid and transparent, and is of normal macroscopic appearance; it does not form a fibrin web on standing.

The cell count in sixty-three examinations was within normal limits.

The albumin showed an increase to a slight or moderate degree in twenty-seven of thirty-four fluids. This increase bore a definite relation to the extent of paralysis, being limited practically entirely to patients with a generalized involvement.

The sugar was normal in all fluids.

The chlorides were determined in thirty fluids, with results ranging from 7.1 to 8.5 gm. per liter, the average being 7.55 gm. In thirteen fluids values were obtained slightly above the normal range.

The permanganate index was determined in fifteen examinations, and showed an index ranging from 1.0 to 3.5 with an average of 2.3.

The meningeal permeability to sodium nitrate was studied in twenty-three fluids. In twenty, the normal figure of 10 mg. or below, was the value found, while in three a slight increase of permeability seemed indicated by the figure of from fifteen to twenty mg. per liter.

The examination for acetone was carried out in thirteen fluids, and in only three was a positive reaction found. Two of the moderate reactions occurred in fatal cases in which the fluid was taken from desperately ill children within a few days of death. The other was in a patient with generalized paralysis and pronounced cachexia, in whom the reaction was only one plus.

In a previous study of twenty-eight fluids the colloidal gold reaction gave a reduction constantly in the first five or six tubes of the luetic zone in 27 patients with generalized paralysis. In one fluid from a patient with local paralysis, the reaction was negative. As the patient improved clinically, the reaction seemed to subside.

The colloidal benzoin reaction was performed on twenty-eight fluids. Three fluids were from patients with purely local paralysis of the palatine type, and in all of these, the benzoin reaction was negative. Ten fluids were from cases in which a local paralysis was accompanied by suggestive generalized involvement, and here a slight reaction in two tubes (8 and 9) was present.

Alcoholic Psychoses

In alcoholic psychosis the quantity of fluid that can be removed in one sitting is greatly increased, it often being possible to remove as much as 30 to 40 c.c. easily. The pressure is greatly increased in this type of psychosis, running, as a rule, from 150 to 300 mm. of water in height. The fluid is clear and colorless; the protein is not increased, and the cells are usually normal both in number and type, although occasionally I have noticed an increase in the cell count ranging from 26 to 30 cells per cubic millimeter.

In the psychoses coming on soon after the acute alcoholic stage, as in delirium tremens, alcohol may be present in the cerebrospinal fluid. The determination of the amount of alcohol present in the cerebrospinal fluid has been suggested by Bogen as a test for the degree of drunkenness. In the late alcoholic hallucinoses coming on weeks after the debauch, alcohol is absent from the cerebrospinal fluid.

Manic-Depressive Psychoses

The cerebrospinal fluid is negative in every respect.

Weston and Howard found no changes in the sodium, potassium, magnesium and calcium content of the cerebrospinal fluid in manic-depressive insanity in the manic and in the depressive states.

Dementia Precox and Paranoia

Dementia precox gives a normal fluid as a rule. Occasionally the pressure and glucose content are increased. Paranoia usually shows no deviation from the normal.

Hemorrhage of the Brain

Cerebrospinal fluid removed soon after the hemorrhage occurs is bright red in color due to the admixture of the blood, and contains many red and white blood cells. Fluid from cases of hemorrhage of old standing is yellow (Xanthochromia) and contains only few cells. There are some cases of hemorrhage of the brain in which the blood does not reach the subarachnoid space, in which case the fluid is colorless. In cases of recent hemorrhage the fluid is increased in amount and pressure. In hemorrhages of old standing the amount and pressure of fluid are not increased as a rule. The globulin may or may not be increased. The serum albumin is usually increased due to the blood in the fluid. Cholesterol is present in appreciable amounts.

Skull Fracture

The fluid may be blood-tinged if meningeal hemorrhage has occurred; otherwise the fluid is clear. The amount and pressure of the fluid is as a rule unaltered unless a meningitis or an irritation of the meninges follows the fracture, in which event the cerebrospinal fluid pressure is elevated. This often occurs in connection with depressed fractures.

Pachymeningitis Hemorrhagica Externa

The cerebrospinal fluid is normal in this condition.

Pachymeningitis Hemorrhagica Interna

The cerebrospinal fluid may be clear and colorless, or it may be yellow. The pressure may be slightly elevated. There may be a slight pleocytosis, although the cell count is usually normal. The globulin may be slightly increased in amount. The cerebrospinal fluid may give a positive benzidine test although red blood cells are absent. The Lange test is negative.

Cerebral Thrombosis

The fluid may have a yellowish tinge and the cell count and globulin content may be slightly increased. Generally, however, the fluid is normal.

Encephalitis

The cerebrospinal fluid changes differ with the type of encephalitis. In lethargic encephalitis, the fluid is usually increased in amount and pressure. The cells are increased. The globulin is usually increased. The sugar is occasionally increased, but as a rule is normal. The chlorides are normal. These points serve as aids in differentiating encephalitis from meningitis where the cerebrospinal fluid chlorides and sugar are practically always decreased. The Lange often shows a discoloration in the luetic zone.

In encephalitis secondary to some infectious disease, the cerebrospinal fluid changes depend on the meningeal reaction. As a rule the meningeal reaction is only slight. The fluid is then slightly increased in amount and in pressure, the cells are only slightly increased in number, varying between 10 to 12 per c.mm.

Finally there is a type of encephalitis in which the cerebrospinal fluid is normal in every respect although clinically there is paralysis of one or more extremities. I have seen three such cases lately. The negative cerebrospinal fluid findings, I believe, may be explained by a lack of meningeal reaction in these cases.

Occasionally an acute hemorrhagic encephalitis is encountered. Reference to cerebrospinal fluid in this condition is very scanty. In the case of Norris, the fluid removed by means of lumbar puncture was under increased pressure and the cell count was 1,250, practically all red cells.

In encephalitis secondary to lead or arsenic poisoning, these chemicals may be present in the cerebrospinal fluid.

Abscess of the Brain

In the early stages the fluid is usually clear and under slightly increased pressure. The cells range between 9-10 per c.mm. The globulin may be slightly increased and the Lange may show a discoloration in the syphilitic zone. Neustaedter et al. report a rise in the calcium content of the cerebrospinal fluid in this condition.

In the terminal stages of brain abscess, a secondary meningitis may develop with corresponding changes in the fluid such as many cells and a positive globulin. At times the secondary meningitis is localized to the part of the brain in which the abscess is located. Occasionally it happens that the abscess breaks through the cortex of the brain and is emptied into the subarachnoid space. In that case the fluid is turbid, the cells are greatly increased and are mainly polymorphonuclear leucocytes, and even organisms originally causing the abscess may be present in the cerebrospinal fluid. The following cases illustrate the character of the fluid in brain abscess:

M. G.—Had influenza-pneumonia several months before entering hospital. Fell off 1 story 2 months before. Admitted to hospital in coma with a temperature of 99° F. Recovered consciousness and went into coma again. Kernig, Brudzinski and Babinski signs were positive at times. There was also a rightsided paralysis.

The cerebrospinal fluid drawn by lumbar puncture was clear and under marked pressure. It contained nine cells per c.mm., all of which were small lymphocytes. The globulin was slightly positive. Sulphosalicylic acid produced a slight turbidity, mercuric chloride also gave a slight turbidity, but settled in a few minutes in a rather heavy precipitate. After 24 hours the mercuric chloride precipitate remained heavy and the sulphosalicylic precipitate was very small. The chloride reading was 850 mg. per 100 c.c. The Lange test was negative.

A second lumbar puncture was done 4 days later. The fluid was clear but under less pressure than the first time. The cell count was 10 all of which were lymphocytes. The globulin test was slightly positive. The chloride was 850 mg. per 100 c.c.

The patient became gradually worse. A decompression operation was performed and a large temporal abscess was found on the right side.

W. D.—Brain abscess. Cerebrospinal fluid was clear and under pressure. Cell count was 25 and consisted of 90 per cent small lymphocytes and 10 per cent large lymphocytes. The globulin was negative. Lange test was also negative.

Parasitic Cysts of the Brain

Cysticercus cells may occasionally be found in the cerebrospinal fluid in this condition according to Eskuchen.

Tumor of the Brain

In tumors of the brain, the amount of cerebrospinal fluid obtainable may or may not be increased, depending on whether or not the foramen of Magendie is blocked and on how much irritation of the meninges is present; the cells are usually slightly increased in number, ranging between 10 to 15 per c.mm. Most of the cells are small mononuclear in type. Occasionally, however, they are large lymphocytes. The cells may occur in clumps. In cases of carcinoma or sarcoma of the brain or meninges, tumor cells may be seen in the cerebrospinal fluid. The globulin as a rule is not increased but may be slightly increased. The Lange test may show changes in the 3rd, 4th and 5th tubes (0044230000). Cholesterol may be present in appreciable amounts. Saponin hemolysis of red blood cells is usually inhibited.

Table LV, taken from Freemont-Smith and Ayer, shows the main changes occurring in the cerebrospinal fluid from different loci in brain tumor cases and in cases of subarachnoid block.

Tuberculoma

The cerebrospinal fluid changes in tuberculoma may be those of a brain tumor or of tuberculous meningitis. Before the development of tuberculous meningitis, the fluid is increased in amount, the cells only slightly increased in number, and the protein slightly increased. After the development of tuberculous meningitis, the changes are those characteristic of tuberculous meningitis.

Froin's Syndrome (Massive Coagulation)

Froin's syndrome occurs almost exclusively in conditions associated with spinal subarachnoid block, as in chronic

syphilitic spinal meningitis, transverse myelitis due to cord tumors, epidural abscesses or Pott's disease. In this condition, the cerebrospinal fluid below the site of blockage exhibits the characteristic features of xanthochromia and massive coagulation. The most constant feature is the massive coagulation which is due to the presence of an excess amount of protein which is usually 0.5 to 1 per cent. The protein increase is due to the presence of fibrin, globulin and albumin, the greatest increase being in the albumin according to Mestrezat. The cell count may be normal, increased or no cell count may be found. The protein increase is all out of proportion to the increase in cells, an example of albuminocytologic dissociation. The chloride and sugar content are normal or slightly reduced.

Acute Anterior Poliomyelitis

The changes in the cerebrospinal fluid vary with the stage of the disease, and with the reaction of the meninges. In the preparalytic stage, or stage of irritation, the fluid is usually increased in amount and in pressure; the cells vary anywhere between 30 to 70 per c.mm., and are either made up entirely of polymorphonuclear leucocytes, or of both lymphocytes and leucocytes. The foam test is positive. The globulin may or may not be increased. The Lange curve is more or less characteristic in that there is frequently a discoloration in the luetic zone such as 0112100000.

In the second stage, or stage of paralysis, the fluid is still increased in amount and pressure, the cells varying between 50 to 150 per c.mm., usually consisting entirely of lymphocytes. The globulin is distinctly increased, and the Lange curve is about the same as in the stage of irritation.

As pointed out by Lyon, an initial rise in the cell count with polymorphonuclear leucocytes predominating, followed in 24 to 36 hours by a fall in the total cell count with a shifting of the cell count to a relative mononucleosis of 90 per cent or more, is typical for poliomyelitis.

In the third stage, or stage of recession, the fluid gradually returns to normal. It sometimes takes two weeks, and other times two years until the fluid is entirely normal.

The bacteriology of poliomyelitis is still an open question. Flexner and Lewis found a filtrable virus. Mathers, Nuzum and Rosenow report the finding of a micrococcus in the brain and cord. Nuzum reports the presence of the coccus in the cerebrospinal fluid. The organism, according to these authors, is grown best on a 1 per cent glucose

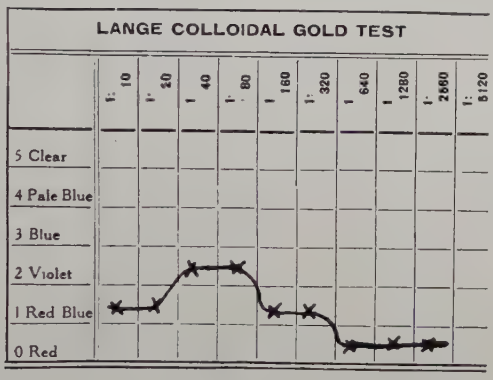

Fig. 87.—Case of epidemic poliomyelitis. First week of disease.

broth medium, incubated under aerobic conditions. Other workers dispute the specificity of this microorganism in poliomyelitis. At the present state of our knowledge no positive diagnosis can be made of poliomyelitis by the fluid findings alone. The history of the case and its progress must also be taken into consideration.

The following case might help illustrate the changes taking place in the cerebrospinal fluid of poliomyelitis:

R. E., sick three days with radiating pains in the lower extremities. The cerebrospinal fluid was clear and came out under great pressure. The cell count was 300; 90 per cent of which were lymphocytes and 10 per cent polymorphonuclear. Noguchi positive, Ross-Jones and Nonne negative. Mercuric chloride gave, at the end of 24 hours, double the amount of precipitate of sulphosalicylic acid. The Lange gave a violet discoloration in the first two tubes. The culture was negative. The patient developed a paralysis on the 4th day of the disease.

Table LXVI

Cerebrospinal Fluid Findings in Various Conditions

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
			(Number of c.c. easily removed)			(Number per c. mm. and type)						
Normal	None	Clear	5-10	90 mm. of water in child. 150 mm. in adult	None	1-6 Small lymphocytes	Less than 2	No	50-100 mg.	Negative	Negative	
Uremia	None	Clear	Normal or Increased	Increased	None	Normal	2 or over	Slight or marked	Normal	Negative	Negative	Urea may be increased. Chlorides occasionally increased.
Diabetes	None	Clear	Normal	Normal	None	Normal	2 or over	No	Above 100 mg.	Negative	Negative	Acetone may be present.
Skull fracture (without meningeal hemorrhage).	None	Clear	Normal or greatly increased	Normal or Increased	None	Normal	Less than 2	No	Normal	Negative	Negative	
Meningeal hemorrhage (a) bloody	None	Bloody	Increased	Increased	Bloody	Many red and white	Above 2	Yes	Normal	Negative	Negative	Cholesterol present. Serum albumin in large quantities.
(b) clear (Old standing)	None	Clear	Normal or Increased	Increased	None	5-10 small lymphocytes	2 or over	Slight	Normal	Negative	Negative	Cholesterol present. Serum albumin may be present in large quantities.
Lateral sinus thrombosis	None	Clear	Normal or Increased	Increased	None	Normal	Normal	No	Normal	Negative	Negative	Queckenstedt sign.
Brain tumor	None	Clear	10-15	Slightly increased	None	10-15 Small or large lymphocytes	Normal	Slight	Normal	Negative	Occasionally 0442-300000	Inhibition of hemolysis described by Hauptmann. Increased cholesterol.

TABLE LXVI—CONTINUED

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
Brain abscess (a) not ruptured	None	Clear	Slightly increased	Slightly increased	None	10-15 Small lymphocytes. Occasionally large lymphocytes	Normal	Slight	Normal	Negative	Occasionally 0444-300000	
(b) ruptured	Any organism	Turbid	Increased	Increased	Yes	Several thousand polymorphonuclear leucocytes	Above 2	Marked	Normal	Negative	000000-4444	Organisms may be present.
Spinal cord tumor	None	Yellow (Xanthochromia)	Decreased	Decreased	Coagulates spontaneously	None or 1-2	Above 2	Marked	Normal or decreased	Negative		Chlorides may be decreased.
Syphilis of central nervous system (a) Gen. Paresis	None	Clear	10-40	Increased	None; Occasionally small flocculi	40-200 Small lymphocytes	Normal	Marked	Normal	Positive	555550-0000 (Paretic curve)	
(b) Cerebrospinal syphilis	None	Clear	Increased 15-30	Increased	None	100-200 Small lymphocytes	Normal	Yes	Normal	Positive	005555-0000	
(c) Tabes dorsalis	None	Clear	Increased	Increased	None	60-180 Small lymphocytes	Normal	Yes	Normal	Positive	005550-0000 (Tabetic curve)	

TABLE LXVI—CONTINUED

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
(d) Juvenile paresis	None	Clear	Increased	Increased	None	40-80 Small lymphocytes	Normal	Yes	Normal	Positive	555550-0000	
Meningism	None	Clear	Increased	Increased	None	Normal or slightly increased	Normal	No or slight	Normal	Negative	Negative	
Epidemic encephalitis	Minute filterable virus described by some authors	Clear	10-30	Increased	None	10-20 Small mononuclear	Normal	Slight	Normal or increased	Negative	Negative	
Anterior poliomyelitis	Micrococcus described by some authors	Clear	Increased	Increased	None	10-100 Polymorphonuclear very early, mononuclear after second day	Normal	Yes	Normal	Negative	Luetic zone early. Meningitic zone later	
Tuberculous meningitis	Tubercle bacilli	Clear or slightly opalescent	Increased	Increased	Fine pellicle	30-400 Mononuclear	Above 2	Yes	Decreased	Negative	Between luetic and meningitic zones (000023-3000)	(1) Cataphoresis to the anode. (2) Sulphosalicylic precipitate 3-6 mm. Bichloride of mercury 6-20 mm. (3) Guinea pig inoculation shows tubercles. (4) Chlorides decreased to 600 mg. per 100 c.c. or below.

TABLE LXVI—CONTINUED

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
Meningococcus meningitis	Meningococcus	Turbid	Increased	Markedly Increased	Thick, varying with stage of disease	50-8000; 95% Poly's; Endothelial cells present	Above 3	Marked	Absent or greatly diminished	Negative	Meningitic zone 00000-45555	(1) Cataphoresis to the cathode. (2) Agglutination of bacteria by specific serum. (3) Precipitation of fluid with antimen. serum (4) Sulphosalicylic acid 7-20 mm., Bichloride 5-6 mm. (5) Chlorides slightly decreased.
Pneumococcus meningitis	Pneumococcus	Turbid	Increased	Increased	Present	50-8000 98% Poly's	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Agglutination. Sulphosalicylic 7-20 mm.; Bichloride 5-6 mm.
Streptococcus meningitis	Streptococcus	Turbid	Increased	Increased	Yes	50-1000 98% Poly's	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Sulphosalicylic 7-20 mm. Bichloride 5-6 mm.
Influenza meningitis	Influenza bacillus	Turbid	Increased	Increased	Yes	50-1000 98% Poly's Occasionally 50% lymphocytes	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Sulphosalicylic 7-20 mm. Bichloride 5-6 mm. Indol test described.
Other Meningitis	Specific organism	Turbid	Increased	Increased	Heavy	50-1000 98% Poly's	Above 2	Increased	Normal or diminished	Negative	Meningitic zone	

Multiple Sclerosis

In this condition the cell count is usually normal, although there may be an increase up to 20 cells per cubic millimeter. There may or may not be a slight increase in the globulin. The most common finding is a Lange curve of the paretic type in about 50 per cent of the cases. In all other respects the fluid is normal.

Amyotrophic Lateral Sclerosis

Mestrezat found an increased sugar content in one case of amyotrophic lateral sclerosis and an increase in cells and protein in another case. Eskuchen found a mildly positive globulin reaction. In all our cases the fluids were absolutely normal.

Syringomyelia

The cerebrospinal fluid is usually normal. Mestrezat found an increase in protein and sugar content in one case.

Paralysis Agitans

Fatten reports a reduction in the middle tubes in the Lange reaction in seven out of ten cases. Otherwise the fluid is normal.

Subacute Combined Degeneration of the Cord

Except for an inconstant and slight rise in the cell count and globulin content, the cerebrospinal fluid is normal.

Spinal Muscular Atrophy

Eskuchen and Mestrezat found an increase in the pressure of the cerebrospinal fluid, but no other changes.

Cerebral Arteriosclerosis

There may be an increase in the cells and in the protein content of the cerebrospinal fluid, the increase being greater in those conditions where encephalomalacia is also present. The sugar content may be elevated.

Other Degenerative Conditions

In the other degenerative conditions such as bulbar paralysis, Friedreich's ataxia, Thomsen's disease, etc., there are no uniform changes in the cerebrospinal fluid.

ACUTE INFECTIOUS DISEASES WITHOUT ORGANIC INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

Do the various acute infectious diseases produce any changes in the cerebrospinal fluid, and if so are the changes characteristic for the respective diseases? The reports in the literature are not uniform. Herrick and Dannenberg, for instance, found some variation in the cerebrospinal fluid of one-third of the seventy-six cases of acute infectious diseases studied by them. Their series included lobar and bronchopneumonia, influenza, tonsillitis, parotitis, arthritis and the exanthemata. Johnston found no variations from the normal in this type of case. In only one case of his series was a pleocytosis present.

The determining factor, I believe, is the meningeal reaction, which expresses itself in the cerebrospinal fluid. The greater the meningeal reaction, the more marked the cerebrospinal fluid changes. Accordingly, no set rule can be given as to the cerebrospinal fluid in a certain infectious disease. The findings will depend on the presence or absence of a reaction, and on the degree of reaction, of the meninges.

Meningism

In many infectious diseases, notably pneumonia, grippe, otitis media and also in some cases of intestinal intoxication, there are often symptoms of cerebral irritation, simulating a meningitis, although no bacteria are found in the fluid and no meningeal exudate makes its appearance. To cases of this character, Dupré has given the name of meningism. The fluid in these conditions is generally increased

in amount, sometimes even to the same extent as in a severe case of meningitis. The pressure of the fluid is also higher than normal. The color, however, is unchanged. The cells at times are increased. Often, however, they are not. The globulin, as well as the bacteriologic, tests are usually negative. Only occasionally is there an increase in the globulin. Caution, however, must be exercised not to make a premature diagnosis of meningism in all instances of negative findings of the fluid, for it frequently happens that cases of meningitis and poliomyelitis in the early stages of the disease, give no other changes in the cerebrospinal fluid than an increase in the amount of the fluid.

A comprehensive bibliography covering the subject to 1903 has been collected by Beck. Numerous papers, an example of which are the papers of Mautner and Baboneux, have appeared since. As pointed out above, the cerebrospinal fluid changes in meningism are still an open question. I deem it best to review the literature on the cerebrospinal fluid in each infectious disease, so as to present both sides of the question.

Pneumonia

Voisin performed 49 lumbar punctures in 45 cases of lobar or bronchopneumonia with meningeal symptoms. Forty-four cases had purulent otitis media. There was an increase in cells in 8 fluids, the number of cells varying between 11 and 66 per c.mm. Routine spinal punctures were performed by Rohdenburgh and Van der Veer in a series of pneumonia cases irrespective of the occurrence of meningeal symptoms. In this series, of those dying, 14 (87 per cent) had pneumococci in the cerebrospinal fluid on culture, while 2 (13 per cent) had none; in contrast, of those recovering, 15 (34 per cent) gave positive cultures, and 28 (66 per cent) were negative. All of the fluids giving positive cultures were positive for both sugar and globulin. The average cell count in those dying was 214, while in

those recovering it was 50. The fluids negative to culture showed a very slight increase in cells (30), but were otherwise normal. In but one instance of the entire series was the fluid of such character that it might be termed purulent, and this was the only case showing meningeal symptoms. All of the patients showing positive cultures were profoundly depressed, reacted badly to the infection, and for the most part, were markedly delirious.

As a result of their survey, the authors believe that pneumococci are present with much greater frequency in the cerebrospinal fluid than is usually thought to be the case, without the presence of meningeal symptoms.

McLean and McIntosh studied the cerebrospinal fluid in 20 infants suffering from bronchopneumonia, all of whom had some symptoms of meningeal irritation such as rigidity of the neck, vomiting, drowsiness, coma or convulsions. The fluid was clear and colorless in all these cases. In one case the globulin was positive, in two cases questionable, and in twelve cases negative. The highest cell count was 12, the average count being four cells. The sugar was normal. The chlorides were also within the normal range.

Mumps

The association of mumps with meningeal symptoms has given rise to the term "mumps-meningitis." Whether the meningeal symptoms occasionally accompanying mumps are characteristic of the mumps or are just coincidental, is open to question. My belief is that the latter is true. The following report by Feiling of the cerebrospinal fluid in a case of mumps occurring in a child five and one-half years of age, is characteristic of the reports in the literature:

"Fluid colorless, slightly turbid, under slightly increased pressure. Chemical examination: albumin, 0.125 per cent; globulin, no ring with ammonium sulphate; sugar reduction only just perceptible. Cytological examination: cells numbered 2500 per cubic millimeter. Differential count: lymphocytes 96 per cent; polymorphonuclears, 2 per cent;

endothelial cells 2 per cent. Bacteriologic examination: no organisms seen in films. No growth on culture in 24 hours."

Pertussis

In an uncomplicated case of pertussis the cerebrospinal fluid is increased in amount and in pressure without any other changes. In the presence of an encephalitis, which not infrequently accompanies pertussis, the cerebrospinal fluid changes are those that characterize most encephalitides; namely, increase in cell count and in globulin.

Scarlet Fever

Gauss examined fluid from fifty patients who suffered from scarlet fever or associated exanthemata in patients varying in age from one to fourteen years, mostly under seven years. The cell count varied from 1 to 20 cells averaging 8 cells, lymphocytes predominating.

Typhoid

In the case of a child suffering from typhoid fever with meningeal reaction, Fontecilla and Sepulveda found the chlorides reduced to 620 mg. and the glucose to 20 mg. without any other change in the fluid. The blood gave a positive Widal reaction. In seven cases of typhoid fever without meningitis Mestrezat found the glucose slightly reduced in all (40 to 45 mg. per 100 c.c.). The amount of chloride varied from 670 to 780 mg.

Meningitis Sympathica

The condition called by Strauss "meningitis sympathica" occurs occasionally in the course of an acute otitis media, mastoiditis, or other infection about the head. It resembles a meningism with the exception that the protein and cell contents of the cerebrospinal fluid are increased. The cells are usually polymorphonuclear leucocytes, although the fluid is sterile.

Acute Mastoiditis, Otitis Media and Sinusitis

Infections about the cranium usually cause a more marked meningeal reaction than infections in other parts of the body. This is probably due to the proximity of the infection to the meninges. It is therefore not unusual to find changes in the cerebrospinal fluid in the course of an acute mastoiditis, otitis media or sinusitis. These changes may be limited to an increase in cerebrospinal fluid pressure, as occurs in meningism or may include an increase in the globulin content and cell count, due to a meningitis sympathica.

Of course, if a secondary brain abscess or encephalitis of meningitis develops, the changes in the cerebrospinal fluid are those typical of these respective conditions.

Lateral Sinus Thrombosis

The characteristic finding in this condition is an absent or altered Queckenstedt sign on the affected side; that is, compression of the external jugular vein on the affected side will cause no rise, a smaller rise or a slower rise in the cerebrospinal fluid pressure than compression of the external jugular vein on the unaffected side.

Serum Meningitis

Following the injection of sera intrathecally, the clinical picture of a meningitis often develops in the course of a serum reaction. The protein and cell counts are increased. In one case I saw a turbid fluid with positive globulin test and several thousand polymorphonuclear leucocytes, cultures of which were sterile. Lavergne and Abel observed an increase in pressure, sugar, lymphocytes and polymorphonuclear leucocytes, with a normal globulin. At the onset of the eruption the cell count falls below normal, then rises above normal and finally returns to normal.

GENERAL AND METABOLIC DISEASES

Uremia

The fluid is often increased both in amount and pressure, especially in the convulsive type of uremia. The cells are not increased in number. The globulin may or may not be increased. The serum albumin is usually increased. The chlorides are often increased to 800 or 850 mg. per 100 c.c. of fluid. The urea nitrogen is greatly increased in amount, reaching as high as 55 mg. per 100 c.c., anything above 50 mg. usually being fatal. According to Futh and Lockemann, lactic acid is present in the fluid in large amounts.

In chronic nephritis without uremia, the chlorides and nitrogenous elements of the cerebrospinal fluid are increased in proportion to their increase in the blood.

Diabetes Mellitus

The cerebrospinal fluid is usually normal in amount, in pressure, and cell count. The amount and pressure may, however, be increased, especially during diabetic coma. It is chemically negative in all respects but in its sugar content, which is greatly in excess of normal. Foster found the sugar in the fluid of 12 cases of diabetes to vary between 0.5 per cent and 3 per cent. My highest reading was 0.38 per cent. In one case I found the sugar content in the cerebrospinal fluid to be even higher than that of the blood. Acetone and diacetic acid may also be found in large amounts in the cerebrospinal fluid of diabetics with acidosis. These two substances usually indicate a grave prognosis.

Jaundice

Even in severe jaundice, the cerebrospinal fluid usually contains no bile pigments. Occasionally, however, they may be present. In this event the cerebrospinal fluid will be tinged yellow and the presence of bilirubin demonstrable by the Van den Bergh test.

Trichinosis

The fluid is clear and under slightly increased pressure. There is no increase in the cells or globulin. Motile trichinae may occasionally be seen in the centrifuged fluid during the stage of dissemination.

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CHAPTER XV

CEREBROSPINAL FLUID IN INFANTS AND CHILDREN

Does cerebrospinal fluid differ with the age of the patient during health and during disease? The only way to tell would be to do a series of punctures on one and the same individual from birth to old age, an unjustifiable procedure. That variations in the cerebrospinal fluid do occur with age may be inferred from an occasional reference in the literature. Bernhard, for instance, found the uric acid content of cerebrospinal fluid to be higher in children than in adults. It has been noted by Roberts that the color of cerebrospinal fluid in the normal newborn is yellow, while in the older child it is colorless.

I have observed that in the newborn the rate of flow of fluid through the spinal puncture needle is less than in older infants or children. It is from such casual observations that one is led to believe that there is a possible relationship between age and cerebrospinal fluid.

In the following pages I shall discuss cerebrospinal fluid in infants and children under three headings:

1. Does cerebrospinal fluid in normal infants and children differ from that in normal adults?

2. What changes occur in the cerebrospinal fluid in diseases peculiar to infancy and childhood, as in cerebral hemorrhage of the newborn, hydrocephalus, amaurotic family idiocy, Mongolian idiocy, spasmophilia, congenital syphilis, and chorea?

3. Does the age of the patient influence the cerebrospinal fluid changes in one and the same disease? For instance, are the cerebrospinal fluid findings in meningitis occurring in children, different from the cerebrospinal fluid findings in meningitis occurring in adults?

CEREBROSPINAL FLUID IN NORMAL NEWBORN, IN INFANTS, AND IN CHILDREN

Normal Newborn

The amount of fluid obtainable from the newborn in the first twenty-four hours of life is smaller than that obtainable in older children. The amount obtained by me by means of lumbar puncture varied between a few drops and 5 c.c. with an average of 3 c.c. By cistern puncture I obtained between 1.5 to 10 c.c. with an average of 6 c.c. By ventricular puncture I obtained from 2 to 5 c.c.

The reports from various workers on cerebrospinal fluid pressure in the normal newborn have varied but little. Sidbury found it to be between 2 and 5 mm. of mercury. Munro found it to be between 2 and 6 mm. of mercury. In my series, which included about 60 per cent of xanthochromic fluids, the spinal pressure varied from 1 to 6 mm. of mercury, and the cistern pressure varied between 4 to 40 mm. of mercury.

The color of the cerebrospinal fluid in the normal newborn has been a matter of dispute. Roberts believes that the fluid in all normal newborn is yellow, and that the yellow color is due to bile. Sharpe and Maclaire found clear cerebrospinal fluid in about 95 per cent of their cases. A great number of the fluids obtained by me from newborn were xanthochromic.

Some of these gave a positive benzidine reaction, some a positive Van den Bergh test, and in some both of these tests were negative. However, necropsies from patients who had xanthochromic fluid showed some cerebral hemorrhage. This makes me believe that cerebrospinal fluid from normal newborn is colorless, and that when it is yellow there has been a cerebral capillary exudation, the yellow color being due to a pigment intermediary between hemoglobin and bilirubin, which gives neither a benzidine nor a Van den Bergh reaction. This makes me believe further

that many newborn infants have a capillary hemorrhage or exudation of a small amount of blood at the base of the brain. The amount of blood in most cases, however, is so small that it produces no clinical symptoms and most likely would not be recognized without a spinal puncture. Glaser also found xanthochromic fluids in premature infants which gave neither a positive benzidine nor a Van den Bergh test.

Normal Infants and Children

The term normal, as pointed out elsewhere, is only relative, as seldom, if ever, is cerebrospinal fluid removed from an entirely normal person. As a rule, the patient from whom the fluid is removed presents some symptoms of meningeal irritation, but is later found to be suffering from some other condition. The term normal, therefore, applies to fluid removed from persons who have no organic pathology of the central nervous system, but who may be suffering from some pathology somewhere else in the body, with some temporary irritation of the central nervous system.

The cerebrospinal fluid in normal infants and children is practically the same as in adults. It is clear, colorless, and contains no globulin. The pressure of the fluid in children has been found by Quincke and myself to be less than in adults, being 45 to 90 mm. of water in the former and approximately twice as much in the latter.

Peterman found the cell count in normal children to be 0 to 6 lymphocytes. McLean and McIntosh state that in infants cell counts as high as 20 lymphocytes are normal. Stewart compared cerebrospinal fluid from different loci in normal children. In the lumbar fluid, he found cell counts ranging from 34 per c.mm. at seven days to 3 per c.mm. at twelve years; in cisternal fluid, ranging from 28 cells at eleven weeks to 3 cells at twelve years; and in ventricular fluid, an average of 0 to 2 cells at all ages. The cells were all lymphocytes, 94 per cent being small lymphocytes.

TABLE LXVII

CEREBROSPINAL FLUID IN NORMAL INFANTS AND CHILDREN

CONDITION	COLOR	AMT. OBTAINED BY SPINAL PUNCTURE	PRESSURE (SPINAL)	CELLS (PER C.MM.)	GLOBULIN	REMARKS
"Normal" newborn	Clear	Few drops to 5 c.c.	1 to 6 mm. mercury	1 to 6	Negative	Amount withdrawn by cistern puncture varies between 1.5 to 10 c.c. Pressure 40 mm. of mercury
"Normal" infants and children	Clear	5 to 10 c.c.	3 to 6 mm. of mercury	1 to 6	Negative	According to Bernhard the uric acid content is higher than in fluid from adults

The chemical composition of the cerebrospinal fluid in infants and children is practically the same as it is in adults. The chlorides, however, according to various workers vary within the wide limits of 600 and 700 mg. per 100 c.c. as compared to the relatively constant finding in adults between 700 and 740 mg. per 100 c.c.

Bernhard states that the uric acid content in the fluid of children is higher than in that of adults, being only 0.54 mg. per 100 c.c. in the latter to 0.78 mg. in the former.

Frequently, one is able to obtain a greater amount of cerebrospinal fluid from a so-called normal child than from a normal adult. This may be due to the fact that the meningeal reactivity of a child is greater than in an adult.

CEREBROSPINAL FLUID IN DISEASES PECULIAR TO INFANCY AND CHILDHOOD

Cerebral Hemorrhage of the Newborn

The cerebrospinal fluid changes in hemorrhage of the newborn depend on the amount and type of hemorrhage. In massive hemorrhage, the fluid is bloody. In basal capillary hemorrhage the fluid is usually xanthochromic, but may be bloody, and occasionally clear. We cannot subscribe to the opinion that the mere presence of blood in fluid indicates cerebral hemorrhage. Subdural puncture is too uncertain a procedure to consider blood in the fluid a diagnostic criterion. The best technician may get bloody fluid.

The amount of protein may or may not be increased. There are usually many red cells. These may, however, be absent. The white cells may or may not be increased.

Hydrocephalus

In most cases of hydrocephalus, the cerebrospinal fluid is normal except for an increase in amount. If, however, the hydrocephalus follows a meningitis, the fluid may show some cytologic and chemical changes and may even con-

tain organisms. Dandy and Blackfan described the phenolsulphonephthalein test for differentiating communicating from noncommunicating hydrocephalus. They inject a known amount of neutral phenolsulphonephthalein into the ventricles of the brain and then do a lumbar puncture. If the hydrocephalus is communicating, the dye will appear in the lumbar fluid within three minutes.

If a known amount of the dye is injected into the spinal canal (or into the ventricles, if there is a communicating hydrocephalus) and the amount of it excreted into the urine within a given time determined, the degree of communication in a hydrocephalus can be estimated.

The method of Dandy and Blackfan is useful but is not always necessary. As a rule the mere attempt to remove the fluid by lumbar puncture will differentiate the types of hydrocephalus. If cerebrospinal fluid is obtained by lumbar puncture, it indicates that the hydrocephalus is communicating. If very little or no fluid is obtained, the hydrocephalus is noncommunicating.

Mitchell and Zeligs described a method by which the amount of fluid in the venrticles can be determined in obstructive hydrocephalus.

Spina Bifida

If there is an associated meningocele the fluid is very turbid and the protein is increased in amount. The cells are not increased. If there is no meningocele, the fluid may be clear or turbid. In marked cases, if the neural canal is open, there may be a continuous drip of cerebrospinal fluid from the spinal fistula.

Amaurotic Family Idiocy

In the case reported by Hassin and Parmelee, the fluid was not under increased pressure. The cell count was 7; the Nonne-Apelt reaction was positive. The Wassermann reaction was negative; the colloidal gold test was

0012210000. The sugar content was 80.6 mg. and calcium content, 7.22 mg. The fluid in our series of cases was normal in every respect.

Mongolian Idiocy

In fluids obtained from Mongolian idiots, Stevens found characteristic gold chloride changes in the syphilitic zone. The globulin content was also increased. Pleocytosis, however, was observed only in the fluids in which blood was present. The Wassermann reaction of the fluid was positive in 11.1 per cent (two of eighteen) of the cases. On the basis of the foregoing observations, Stevens believes that Mongolian idiocy is one of the manifestations of congenital syphilis. In our series of cases, the fluids were normal.

Little's Disease

The changes occurring in the cerebrospinal fluid in cases of spastic paralysis due to brain injuries received during birth, depend upon the nature of the injury to the brain and the meninges. If the paralysis is due to a massive cerebral hemorrhage, the cerebrospinal fluid may retain a xanthochromic tinge for several months. If a meningitis coexisted with or followed the cerebral injury, the fluid may be turbid and may contain an increased amount of globulin. Usually, in Little's disease, the cerebrospinal fluid is clear and greatly increased in amount and pressure. The cell count and globulin content are usually not increased.

Convulsions in Infancy

Convulsions are more frequent during infancy than in adult life. The amount and pressure of the cerebrospinal fluid are always increased during a convulsion no matter what the cause. In fact, it is advisable not to remove cerebrospinal fluid during convulsions because of the danger

of producing a herniation of the brain by removing too much fluid. Sometimes, however, removal of fluid is the only means of relieving convulsions, everything else proving futile. The presence or absence of chemical and cytologic changes depends on the cause of the convulsions. If it is due to an acute meningeal involvement, the fluid will naturally show the usual characteristic changes. If there are no organic changes in the meninges or brain, the fluid is normal.

Spasmophilia

During a convulsion the amount of obtainable fluid is increased. The cells and globulin, however, usually show no change from the normal. With the exception of the period of convulsions there are no alterations in the cerebrospinal fluid, even the amount of fluid obtainable being normal.

A large amount of work has been done in recent years on the calcium content of cerebrospinal fluid, with special reference to spasmophilia. Since the blood calcium is diminished in spasmophilia, it was thought probable that the calcium in the cerebrospinal fluid would also be diminished.

The reports on the content of cerebrospinal fluid calcium in spasmophilia are not uniform. Critchley and O'Flynn found only a trace of calcium in one fluid of active infantile tetany compared to 6.2 mg. in normal fluid. In two cases of latent tetany they found 4 and 5.3 mg. per 100 c.c. of fluid. Shih-Hao found the calcium content of cerebrospinal fluid reduced in two cases of active tetany occurring in Chinese girls fifteen and sixteen years of age, and the content returned to normal after treatment with cod liver oil. Wilcox, Lyttle and Hearn found the calcium content of five cases of tetany within normal limits, and independent of the blood calcium.

Nourse, Smith, and Hartman determined the inorganic constituents of cerebrospinal fluid in 17 cases of spasmophilia and found no significant changes from the normal.

In the cases of spasmophilia with convulsions on the day of the first examination, the calcium content of the blood and cerebrospinal fluid was found somewhat lower than the average of the entire series.

A reduction of carbonates in spasmophilia was found by Balint. According to him the CO_2 combining power of the cerebrospinal fluid may be taken as an index of acidosis. In spasmophilia the acidosis of the fluid is not parallel with that of the blood.

Alimentary Disturbances

From time to time, reports have appeared in the literature, of cerebrospinal fluid changes in diarrheal diseases of infants; the claim being made that the H-ion concentration of the fluid is higher in patients suffering from alimentary disturbances. It is also claimed that the sugar of of the cerebrospinal fluid is increased in alimentary disturbances. The work on the fluid in diarrheal disease is debatable because of the inaccuracy of the methods used. As to an increase in dextrose, the explanation of McLean and McIntosh seems plausible: namely, that it is due to dehydration which in turn causes a concentration of the chemical elements of the various body fluids, including cerebrospinal fluid. On the other hand, Blatters and Lederer found that cases of intestinal autointoxication with meningeal irritation may have the same findings, chemical and cytologic, as those of tuberculous meningitis.

Congenital Syphilis

The cerebrospinal fluid in congenital syphilis was studied by several authors. Tezner, for instance, did 62 punctures in 43 children. In 41 per cent fluid changes were present. The Wassermann test was positive in 32 per cent. In my series of cases the findings in the cerebrospinal fluid of congenital lues were not constant, the fluid changes depending mainly on whether or not the cerebrospinal fluid system was involved.

When there is an involvement of the nervous system, which is the case in about 33 per cent of congenital luetics, the Wassermann reaction in the cerebrospinal fluid is positive; the cells in the fluid are increased in number and consist mainly of lymphocytes. The protein tests are positive, and the Lange test gives a reaction in the syphilitic zone.

In juvenile paresis, the Wassermann is positive in 80 to 100 per cent of the cases. The cells, which are mainly lymphocytes, are increased in number. The Lange curve is characteristic, giving a reaction in the paretic zone. If there is no involvement of the central nervous system, the cerebrospinal fluid is negative.

Chorea of Sydenham

From time to time reports have appeared in the literature of cerebrospinal fluid changes in chorea. Dupre and Camus, for instance, found an increase in lymphocytes in one fluid from a patient suffering from chorea; Baboneux found a lymphocytosis in two out of five cases. Thomas and Tinel observed it in three out of five cases.

Richardier, Lemaire and Sourdel found a lymphocytosis in twelve out of fourteen cases and hypertension in ten. In three cases, symptoms were somewhat relieved by puncture. A number of French observers found a positive Wassermann in chorea and because of this finding, argued in favor of the specific nature of chorea. Morse and Floyd did lumbar punctures 20 times on 19 cases. The cerebrospinal fluid was clear in every instance. The pressure was apparently slightly increased in one instance, but was normal in all others. No fibrin clot was ever observed. The number of cells was slightly increased in 3 out of 10 cases. Leopold and Bernhard found no alterations in the chemistry of the cerebrospinal fluid in chorea. In my cases of chorea, the cerebrospinal fluid was negative in every respect.

MENINGITIS

The cerebrospinal fluid changes in meningitis, occurring during infancy and childhood are the same as those occurring in adult life. There is, however, some difference in the bacteriology of the fluid which is due to the greater frequency with which certain organisms attack the meninges of the child. This is especially true in the newborn.

Meningitis of the Newborn

In the newborn, meningitis is far from rare. Dandy and Blackfan believe that intrauterine meningitis is not infrequent and is responsible for many cases of hydrocephalus. Such cases have been described by Sherer, Holt, Koplik and others. Barron has collected 18 such cases from the literature and added one of his own to the series. Seven of those nineteen cases were caused by the colon bacilli, six were caused by the staphylococcus and streptococcus, two by the pneumococcus, and one each by the meningococcus, Bacillus mucosus capsulatus, Bacillus lacto-aerogenes and Bacillus pyocyaneus. Neal believes that since most cases reported have been diagnosed postmortem, the colon bacilli may have invaded the meninges after death. Neal found only three out of fifty cases of meningitis caused by the Bacillus coli during the first three months of life. The changes in cerebrospinal fluid of the newborn with meningitis is the same as in meningitis affecting older children or adults.

Meningitis in Infants and Children

In a review of the cases of meningitis that were treated at the Sarah Morris Hospital between 1908 and 1920, I found the following organisms given in Table LXIX as the causative factors of meningitis in children.

The cerebrospinal fluid changes in meningitis of children are the same as those present in meningitis of adults.

TABLE LXVIII

CEREBROSPINAL FLUID IN DISEASES PECULIAR TO INFANCY AND CHILDHOOD

CONDITION	COLOR	AMT. OBTAINABLE BY SPINAL PUNCTURE	PRESSURE (SPINAL)	CELLS (PER C.MM.)	GLOBULIN	REMARKS
Cerebral hemorrhage of the newborn						
a) Capillary hemorrhage	Xantho-chromic	Normal or slightly increased	Normal or slightly increased	Normal or slightly increased	May or may not be increased	Benzidine and Van den Bergh usually negative
b) Massive hemorrhage	Usually bloody	Usually increased	Usually increased	May or may not be increased	Usually positive	Benzidine positive
Hydrocephalus a) Communicating	Usually clear	Increased	Increased	Normal or increased	Usually negative	Phenolsulphonephthalein injected into ventricles appears in lumbar fluid in three minutes
Hydrocephalus b) Obstructive	May be turbid	Decreased or no fluid obtainable	Decreased or no pressure registered	Absent. May be increased	May be positive	Degree of obstruction may be determined by phenolsulphonephthalein injected into spinal canal
Spastic paralysis following birth injury	Clear	Increased	Increased	Normal	Negative	If the condition followed massive cerebral hemorrhage the fluid may be xanthochromic

TABLE LXVIII—CONTINUED

CEREBROSPINAL FLUID IN DISEASES PECULIAR TO INFANCY AND CHILDHOOD

CONDITION	COLOR	AMT. OBTAINABLE BY SPINAL PUNCTURE	PRESSURE (SPINAL)	CELLS (PER C.MM.)	GLOBULIN	REMARKS
Spina bifida with meningocele	Very turbid	Very small	Decreased	None or normal	Strongly positive	If it is not associated with a meningocele, the fluid may be clear or turbid. The globulin may or may not be increased
Amaurotic family idiocy	Clear	Normal	Normal	Normal	Negative	Globulin may be positive
Mongolian idiocy	Normal	Normal	Normal	Normal	Negative	A characteristic gold chloride curve in the luetic zone was found by one writer
Spasmophilia	Clear	Normal except during convulsions when it is increased	Normal except during convulsion when it is increased	Normal	Negative	The calcium may be decreased or absent but it is usually normal in amount
Congenital syphilis a) Without involvement of central nervous system	Clear	Normal	Normal	Normal	Negative	Wassermann negative
b) Juvenile paresis	Clear	Increased	Increased	Increased	Positive	Paretic curve with gold chloride solution. Wassermann positive
c) Juvenile tabes	Clear	Increased	Increased	Increased	Positive	Tabetic curve with gold chloride solution. Wassermann positive
Chorea	Clear	Normal	Normal	Normal	Negative	Some writers found a cellular increase in the fluid

Serous Meningitis

Quincke first described serous meningitis in 1898 and since that time many such cases have been reported. On reading the literature one gets the impression that most cases of so-called serous meningitis described by the older writers such as Quincke were cases of encephalitis or chronic meningitis. In the more recent writings the term is used synonymously with meningism. As previously stated meningism is a more common concomitant of acute infectious diseases during childhood than in adult life.

Pachymeningitis Hemorrhagica Interna

During the last few years cases of pachymeningitis hemorrhagica in children have been reported by Kowitz, Finkelstein, Rosenberg, Schwartz, and Burhans and Gerstenberger. The cerebrospinal fluid obtained by lumbar puncture is usually clear and under increased pressure. The fluid obtained from the ventricles is bloody or yellowish or brown in color, due to old blood. With the exception of the two cases of Rosenberg in which he isolated a streptococcus in the bloody fluid, no organisms have been demonstrated in the cerebrospinal fluid of pachymeningitis.

TABLE LXIX

FREQUENCY OF VARIOUS TYPES OF MENINGITIS IN CHILDREN TREATED AT THE MICHAEL REESE HOSPITAL BETWEEN 1908 AND 1920

Tuberculous	125
Meningococcus	89
Pneumococcus	21
Streptococcus	3
Influenza	2
Typhoid	1
Unclassified	32

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CHAPTER XVI

INTRATHECAL TREATMENT

Whenever there is a specific remedy for a disease of the central nervous system, it is of the utmost importance that the remedy be brought into direct contact with the central nervous system as early as possible. Even when no specific remedy exists, it may be advisable to introduce some form of medication into the cerebrospinal canal. The injection may be made intraspinally, intraventricularly, intracisternally, or epidurally.

INTRATHECAL TREATMENT OF MENINGOCOCCUS MENINGITIS

The reports of Flexner and his associates, and the experience of most physicians, have established the fact that the best and most successful way of treating meningococcus meningitis is by means of antimeningococcus serum. The mortality of cases of meningitis that received serum has been reduced to one-half, in some epidemics to one-third, of the mortality of cases that received no serum, as is shown by Table LXX from Sophian.

TABLE LXX

EFFECT OF ANTIMENINGOCOCCUS SERUM ON MORTALITY FROM MENINGOCOCCUS MENINGITIS

AUTHOR	CASES TREATED WITH SERUM		CASES TREATED WITHOUT SERUM
	Number	Percentage Mortality	Percentage Mortality
Flexner	1,400	31.4	70-80
Steiner	2,280	37.0	77
Netter	100	28.0	49
Dopter	402	16.44	52.14
Levy	165	18.18	65
Sophian	161	15.5	

The antimeningococcus serum now in use is prepared by repeated injections into a horse of dissolved meningococci (culture autolysate meningococci extract), followed by injections of live meningococcus cultures. The cultures used are of various strains of meningococci, so that the serum is polyvalent.

The serum is tested before it is put up in packages, by one of several methods: the complement-fixation method, the agglutination test, the opsonin content and the animal protection test. In England the agglutination test is used very extensively. In France, the complement-fixation method is the one most generally employed. In America, all four methods are used by various manufacturers. McCoy, Wayson and Corbitt of the United States Public Health Service, accept any serum which passes satisfactorily, either by an agglutination or complement-fixation test, as a suitable serum for therapeutic purposes. It has been found advantageous to test the serum to be used in a given case with the meningococcus obtained from the particular case. Meningococci present so many strains that at times serum will agglutinate several strains of meningococci and still will not agglutinate the particular strain in question.

The antimeningococcus serum is usually preserved with 0.2 per cent to 0.3 per cent of tricresol. The use of this preservative has given rise to a number of objections. Kramer ascribes some of the deaths that had occurred after the injection of antimeningococcus serum to the use of tricresol which he claims has a very depressing effect on the medullary center. It has been found, however, that of the different preservatives used, tricresol exerts the most marked bactericidal effect on the bacteria, and is a much less irritating preservative than chloroform. It is therefore used exclusively in this country as a preservative for antimeningococcus serum.

Whenever a case presents itself that shows signs and symptoms of meningitis, and gram-negative cocci are found

in the smear from the cerebrospinal fluid, no time should be lost in injecting the patient with antimeningococcus serum. We may even go a step further and say that whenever turbid cerebrospinal fluid is obtained, antimeningococcus serum should be injected immediately on the probability that the case is one of meningococcus meningitis. Of late the intravenous injection has been advocated, but even when intravenous injection of serum is employed the serum should also be injected into the cerebrospinal canal if there are indications of the presence of meningitis.

Technic

The following is the technic of intraspinal injection of serum:

A lumbar puncture is done with the patient lying on his side. (The entire procedure is described in detail in Chapter XII.) If the fluid removed is turbid, 15 to 30 c.c. of cerebrospinal fluid is withdrawn, the amount depending upon the pressure of the cerebrospinal fluid. Two vials, each one usually containing 15 c.c. of antimeningococcus serum which have been kept in the refrigerator, are warmed in warm water to 98 or 99° F. The vial containing the serum is attached to a gravity tube made of rubber with a metal tip at the end to fit the lumbar puncture needle (Fig. 88). The tip of the gravity tube is now introduced into the lumbar puncture needle and the vial is lowered slightly to allow the air bubbles that may be present in the gravity tube to escape and the serum is then allowed to run into the spinal canal. The process of emptying the vial should take from 5 to 10 minutes. If more than 15 c.c. of serum is to be administered, the second vial is attached to the gravity tube after the first vial has been emptied, and the fluid allowed to run in, care now being taken that no air bubbles are allowed to enter the gravity tube during the removal of the vial.

If the serum does not flow readily into the spinal canal the vial containing the serum should be lowered to allow the air bubbles to rise to the surface. If this does not bring the bubbles to the surface, squeezing the gravity tube may do it. This should be done very cautiously, however, to

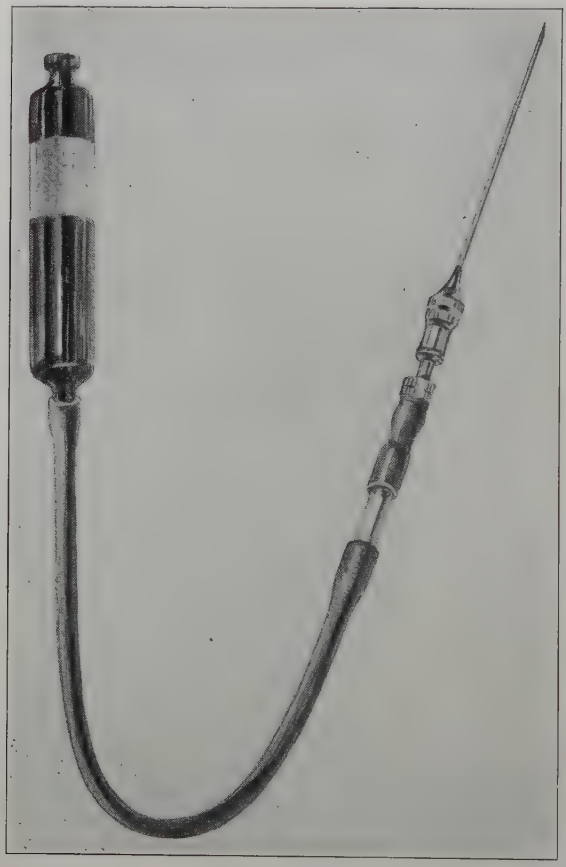

Fig. 88.—Outfit for the introduction of antimeningococcus serum by the gravity method.

prevent the pushing of air bubbles into the spinal canal. If the serum still does not flow into the canal, it is advisable to use a small sterile bulb on the vial to press in the fluid. As soon as all the serum has entered the canal the

needle is withdrawn from the patient's spine and the opening sealed with collodion.

Some authors advise washing the spinal canal with sterile salt solution before the injection of serum. In my opinion this procedure is not necessary.

If serum cannot be injected into the spinal canal, it should be injected either into the cistern, or, in infants, into the ventricles. The procedure consists of the withdrawal of a certain amount of cerebrospinal fluid from the cistern or from the ventricles of the brain (see Chapter XII) and of the injection of the desired amount of serum. Whenever there are signs of a general meningococcemia, such as purpura or arthritic pains associated with meningeal symptoms, antimeningococcus serum should also be injected intravenously. In adults the brachial vein may be used for this purpose. In infants the serum may be injected into the longitudinal sinus.

Dosage

As for the dose of serum to be administered at one time, no absolute rule can be given. Sophian advises the use of blood pressure as an index, a marked fall in blood pressure being an indication to stop the injection of serum. One may always guide himself by the amount of fluid removed, inclining toward the larger rather than the smaller dose. For example, it is best to administer 30 c.c. of serum the first time if it is possible to remove 30 c.c. or more of cerebrospinal fluid. If not more than 15 or 20 c.c. of cerebrospinal fluid can be removed at one sitting an attempt should be made to introduce 20 c.c. of serum. If unsuccessful, at least 15 c.c. of serum should be given. I believe that the principle of giving diphtheria antitoxin, that as much serum as possible be given early, can be applied with the same beneficial effects, to the administration of antimeningococcus serum.

It is unfortunate that the antimeningococcic serum on the market is put up in vials of 15 c.c., two vials to a pack-

age. Since in most cases 30 c.c. of serum is injected it would be less troublesome and more economical to put up 30 c.c. in one vial. It would prevent loss of serum and introduction of air bubbles into the gravity tube and most likely would be less expensive. Recently a concentrated antimeningococcic serum in 10 c.c. vials has been put on the market. This marks an advance in antimeningococcus serum therapy.

How often the administration of serum is to be repeated is also a question that has not yet been definitely answered. However, much can be learned from a study of the cerebrospinal fluid and the clinical course in the particular case. As long as there are bacteria present in the fluid and as long as the cells are numerous and the patient's temperature is high, it is advisable to administer serum twice a day. It has been my plan to administer 30 c.c. of serum the first, second, third and fourth time, at 12 hour intervals; 120 c.c. of serum is thus injected in every case, irrespective of the cerebrospinal fluid findings. Then, if after a wait of one day the temperature continues high and the cerebrospinal fluid contains many cells, I administer 30 c.c. more even if no bacteria are present. I then wait two days longer and if the case shows no change for the better I administer 30 c.c. more. The following case illustrates the method I usually follow:

March 24, 1917, 7 P. M. F. A., two and one-half years of age, was admitted to hospital with symptoms of meningitis.

March 24, 8 P.M. Spinal puncture done, 45 c.c. of cloudy fluid removed under increased pressure and 30 c.c. of antimeningococcus serum injected. Cerebrospinal fluid examination showed 53,280 cells per cubic millimeter, 98 per cent of which were polymorphonuclear. Noguchi, Ross-Jones, and Nonne tests were all positive. Direct smear showed pus cells and gram-negative intracellular diplococci (meningococci).

March 25, 8:30 A. M. Spinal puncture done, 40 c.c. of yellowish cloudy fluid removed under markedly increased pressure; 25 c.c. of serum injected. Examination showed 12,000 cells per cubic millimeter, principally polymorphonuclear. Noguchi, Ross-Jones and Nonne were all positive. Meningococci were found in direct smear.

March 25, 11:30 P. M. Thirty-five c.c. of cloudy, yellowish fluid removed under slightly increased pressure and 25 c.c. of serum injected. Bouillon cultures made March 24 showed meningococci.

March 26. Twenty-five c.c. of cloudy fluid withdrawn and 25 c.c. of serum injected. Few meningococci found in direct smear, no growth appeared on cultures.

March 27. Thirty c.c. of cerebrospinal fluid withdrawn and 25 c.c. of serum injected. Examination showed 85 per cent polymorphonuclear cells, 10 per cent lymphocytes, and 5 per cent mononuclear cell. Globulin tests positive. No growth on cultures.

March 29. Thirty c.c. serum injected. No meningococci found in direct smear and no growth on cultures.

April 2. Cultures made on March 30 and 31, and April 1 and 2 showed no growth.

The following case I believe illustrates the fallacy of administering antimeningococcus serum in too small doses.

D. B., entered the hospital with a history of restlessness, fever, and convulsions. The cerebrospinal fluid removed on entrance to the hospital showed 352 cells per cubic millimeter, all of which were polymorphonuclear. The direct smear showed numerous meningococci. Fifteen c.c. of antimeningococcus serum was administered intraspinally and repeated in 12 hours. A third dose of 15 c.c. of serum was given the next day, making a total of 45 c.c. of serum. Since no organisms could be found in the cerebrospinal fluid withdrawn by the third lumbar puncture and the patient's temperature was down, the physician decided not to administer any more serum. The patient was discharged from the hospital as cured. Two weeks later the patient was readmitted to the hospital with very severe meningeal symptoms. The cerebrospinal fluid was turbid again and showed meningococci. Sufficient serum was administered this time. The child, however, did not improve. The meningitis became more severe and the patient died from the disease. If the patient had received sufficient serum, she would most likely have recovered from the disease and remained well.

Agglutination

In order to make certain that the serum is effective, the organisms obtained from cultures of the cerebrospinal fluid should be agglutinated by the meningococcus serum used for curative purposes. The technic is described elsewhere. The fluid findings and the temperature will also show whether the serum was effective.

Untoward Effects of Serum

There are very few complications that follow the injection of antimeningococcus serum and those that do occasionally present themselves are not severe enough to contraindicate the use of the serum treatment. Among the untoward effects sometimes following the injection may be mentioned:

1. Shock.
2. Aggravation of symptoms—the so-called "serum meningitis."
3. Serum disease.

Shock

Shock occurs in a small percentage of cases. The symptoms consist of respiratory failure, small thready rapid pulse, and contraction of the pupils. The skin is usually pale, cold and clammy, but, occasionally there is a flush of the skin and even edema. Shock can generally be attributed to the too rapid introduction or to the administration of too large an amount of serum or to anaphylaxis. As a matter of phophylaxis it is therefore important that the serum be introduced very slowly and, if possible, in amounts not larger than the amount of cerebrospinal fluid removed. For safety's sake the patient's blood pressure should be watched and the serum discontinued if the fall in pressure is extreme. It has already been pointed out in the discussion of lumbar puncture that it is dangerous to remove cerebrospinal fluid in the sitting position in a patient suspected to be suffering from meningitis, because of the risk of producing shock and even death. When shock does occur, the administration of serum should be discontinued, and atropine in fairly large doses such as 1/300 grain in a child, and 1/100 to 1/50 grain in an adult should be administered hypodermatically. If the atropine does not relieve the symptoms, one c.c. of a 1:1000 solution of adrenalin chloride should be given hypodermatically. The occurrence of shock should not

prevent one from introducing serum intraspinally into the same patient several hours later. In such cases, I would, however, advise the administration of a dose of atropine immediately before administering the serum, so as to prevent the repetition of the occurrence of shock.

Aggravation of Symptoms

Occasionally the patient may become more ill after the administration of serum than he had been before, a condition to which the term "serum meningitis" has been given. The exacerbation of symptoms, however, is only temporary and should not arouse any anxiety.

Serum Disease

Antimeningococcus serum, like every other foreign protein introduced into the body, occasionally gives rise to a rash that makes its appearance several days after the administration of the serum. The rash may be macular or papular, but it occurs most often in the form of large wheals similar to those produced by any other serum. The eruption, as a rule, occurs on the fifth or sixth day after the administration of the first dose of serum. It usually starts from the point of injection of the serum, and spreads upward and downward. It may involve only a portion of the body or the entire body and is accompanied by severe itching. Nausea, vomiting and rise in temperature accompany the rash, but they are generally of very short duration. The appearance of the rash often arouses a suspicion of the coexistence of an acute exanthematous disease such as scarlet fever. However, the history of serum injection and the localization of the rash can generally be depended upon to settle the diagnosis.

In addition, edema of the face and arthritic pains may be present. This condition is self-limited and will pass over in a few days, although the administration of small doses of adrenalin or ephedrine together with soothing lotions locally may alleviate the condition.

INTRATHECAL TREATMENT OF PNEUMOCOCCUS MENINGITIS

Since antipneumococcus serum has been used in the treatment of pneumonia, the use of antipneumococcus serum intrathecally has been suggested in the treatment of pneumococcus meningitis. Broadbent reports four cases of pneumococcus meningitis that resulted in recovery after administration of antipneumococcus serum. He, however, gave the serum to his patient by mouth. Drought and Kennedy consider intrathecal injection of antipneumococcic serum mixed with a solution of sodium oleate as the most promising method of treatment.

Pneumococcus vaccine has been used intraspinally in the treatment of pneumococcus meningitis. The results, however, have not been encouraging.

Optochin (ethyl hydrocuprin) has been administered by Rosenow intrathecally for the treatment of pneumococcus meningitis. I saw one case of pneumococcus meningitis in which intraspinal injections in one-half grain doses of optochin were made and the patient, a child of twelve, recovered. However, the patient had also had an intrathecal injection of antimeningococcus serum previously and this may have been a factor in the recovery, for other cases in which optochin was used, did not respond favorably. One needs to see more than one case of recovery attributable to the use of optochin before he can endorse its use. Those who have used horse serum intraspinally do not report any apparent beneficial results from its use. In general, one cannot make any positive statements about the good effects of intraspinal treatment in pneumococcus meningitis. However, until something better can be found I would advocate repeated lumbar punctures and the injection of serum corresponding to the type of pneumococcus found in the fluid or polyvalent pneumococcus or antimeningococcus serum into the spinal canal.

INTRATHECAL TREATMENT OF STREPTOCOCCUS MENINGITIS

In view of the hopelessness of most cases of streptococcus meningitis, I believe it is worth while giving polyvalent antistreptococcus serum intrathecally. In this connection the case reported by Weaver, in which recovery took place after combined intramuscular and intrathecal injections of antistreptococcus serum, is quite interesting.

INTRATHECAL TREATMENT OF TUBERCULOUS MENINGITIS

Of the numerous remedies advocated and tried in the treatment of tuberculous meningitis, none have been attended with success. Weak solutions of carbolic acid, cresol, iodine and urotropine have been given intrathecally. Tuberculin in various dilutions has also been administered. Recently intraspinal administration of air has been tried by Ramond and Francois. Thus far, neither intraspinal treatment nor any other form of treatment has been of any value in tuberculous meningitis. A few cases have been reported in the literature here and there of tuberculous meningitis resulting in recovery with healed tubercles; however, from the long list of cases that culminated in death, cases reported both in the literature and in hospital records, one is inclined to doubt the diagnosis of "tuberculous meningitis" in cases reported as having recovered.

INTRATHECAL TREATMENT OF INFLUENZA MENINGITIS

Wollstein described a serum for influenza meningitis that is said to be specific. I treated several cases with it without any favorable results.

INTRATHECAL TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS

Rosenow and Nuzum speak very optimistically of the serum treatment of epidemic poliomyelitis. They prepared a serum which they claim is specific against the organism found by them in the brain and cord and also in the cerebrospinal fluid of anterior poliomyelitis. The question of specific serum treatment of poliomyelitis, however, is still a controversial one.

Immune serum is recommended by Netter. The serum must be given early, before the paralytic stage, to be of any avail. Meltzer recommends the intraspinal administration of adrenalin chloride in poliomyelitis. Lewis, who treated 77 cases with adrenalin, reports good results.

INTRATHECAL TREATMENT OF SYPHILIS OF THE NERVOUS SYSTEM

Some workers have reported good results in the treatment of syphilis of the nervous system by introducing neosalvarsan (neoarsphenamine) or sulpharsphenamine into the spinal canal. The general opinion, however, is that intraspinal injections of arsphenamine or of mercury are not only of no value, but carry with them the danger of producing necrosis of the cord. The Swift-Ellis method of treatment has been used extensively. The Swift-Ellis treatment is based on the principle that the blood serum of syphilitics who have been treated with neosalvarsan or sulpharsphenamine has a curative effect, and that the best results are obtained when salvarsanized serum is brought into direct contact with the central nervous system. The method is as follows:

Neosalvarsan or sulpharsphenamine in the proper dose is injected into the patient intravenously, usually into the arm. One hour later 40 c.c. of blood is withdrawn from the patient by means of a dry syringe and needle and collected into a

sterile centrifuge tube. The blood is allowed to coagulate. The following day the serum is centrifuged for one-half hour till all the cells are sedimented. The centrifuge tube must be plugged with sterile cotton or with sterile rubber caps to prevent contamination of the serum. After centrifugation 12 c.c. of serum is carefully pipetted off with a graduated pipette. The serum is diluted with 18 c.c. of normal salt solution, making a total of 30 c.c. of a 40 per cent serum solution. This mixture is heated at 56° C. for half an hour. Then a lumbar puncture is performed, 15 to 30 c.c. of cerebrospinal fluid is removed from the patient and 15 to 30 c.c. of the serum-sodium chloride mixture is warmed to body temperature and injected into the spinal canal. As in any other intraspinal treatment the gravity method of injection should be used here also in order to obviate the danger of shock, although some introduce the serum with a Luer syringe without untoward effects. Another precaution to take is to elevate the foot of the bed one hour after the injection. The patient should remain in bed for at least one day after the treatment. The treatment is repeated once a week, till the Wassermann, Lange and globulin tests on the cerebrospinal fluid become negative, which usually takes four to five weeks.

The Swift-Ellis treatment has many critics. Sachs, for instance, claims that marked paresis and tabes are not influenced favorably by this form of treatment. Halliburton believes that "the intraspinal injection of salvarsan has been abandoned." In spite of the various objections raised, the Swift-Ellis treatment has merit and may be used in selected cases of syphilis of the nervous system. I would only emphasize the great care with which it has to be carried out in order not to infect the patient and thereby set up a suppurative meningitis.

Recently the epidural injection of neoarsphenamine and of distilled water has been used in cases of tabes. Hassin reports favorable results by this method.

INTRATHECAL TREATMENT OF TETANUS

When tetanus antitoxin is used as a prophylactic measure it is usually injected intramuscularly. However, when the disease is fully developed intraspinal injection is indicated. Tetanus antitoxin when injected into the blood has been found to appear only in traces in the cerebrospinal fluid. When injected directly into the cerebrospinal fluid by the intrathecal method, the serum comes directly into contact with the tetanus toxin and has a preventive and perhaps a curative effect; 15-20,000 units should be given at a dose. Although tetanus antitoxin should also be given subcutaneously and intravenously, the intrathecal form of administration is one of the most efficient in the treatment of tetanus, particularly if employed in sufficiently large doses.

The method used in administering the serum is the same as that employed for the administration of meningococcus serum, namely, the withdrawal of cerebrospinal fluid and the injection of the serum by the gravity method, in a somewhat smaller amount than that of the fluid withdrawn. The amount injected may range from 15 to 30 c.c. depending upon the quantity of fluid withdrawn. In the presence of opisthotonus, a general anesthetic may have to be given before the puncture can be performed. Serum shock or sickness may follow the administration of tetanus antitoxin and should be treated like that following injection of any serum. Intraspinal injection of magnesium sulphate in the treatment of tetanus has been advocated by many authors, notably Meltzer. For the control of convulsions, 1 c.c. of a 25 per cent solution of magnesium sulphate per 10 kg. of body weight may be given without fear of respiratory paralysis.

INTRATHECAL TREATMENT OF CHOREA

Chorea has been treated by various authors by intrathecal injections. Lacuna used intraspinal injections of magnesium sulphate. Heiman saw no beneficial results in a case

treated by him with magnesium sulphate. Porter used horse serum. Goodman reported a series of cases which he claimed were benefited by his autoserum treatment, which is administered in the following manner:

The child is put to bed for four days or longer without medication. At the end of this period 45 or 50 c.c. of blood is withdrawn from a vein and rapidly centrifuged. The supernatant blood serum is then pipetted off and kept on ice. A lumbar puncture is made and about 20 c.c. of cerebrospinal fluid is withdrawn. The blood serum is now heated to body temperature and 15 to 18 c.c. of serum is injected very slowly into the spinal canal. The patient should be made to retain the recumbent position for at least one hour after injection. One injection is usually sufficient. Occasionally, however, it is necessary to give two, three, or even four injections.

SPINAL LAVAGE

Lavage of the subarachnoid space by means of normal salt solution may be used in cases where the cerebrospinal fluid is very thick. Lavage may be done either by the insertion of one needle in the cisterna magna and another in the lumbar region or by the insertion of two needles at different levels of the spine. The saline is introduced into the upper needle and flows out through the lower.

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